INTERNATIONAL RECORD OF MEDICINE

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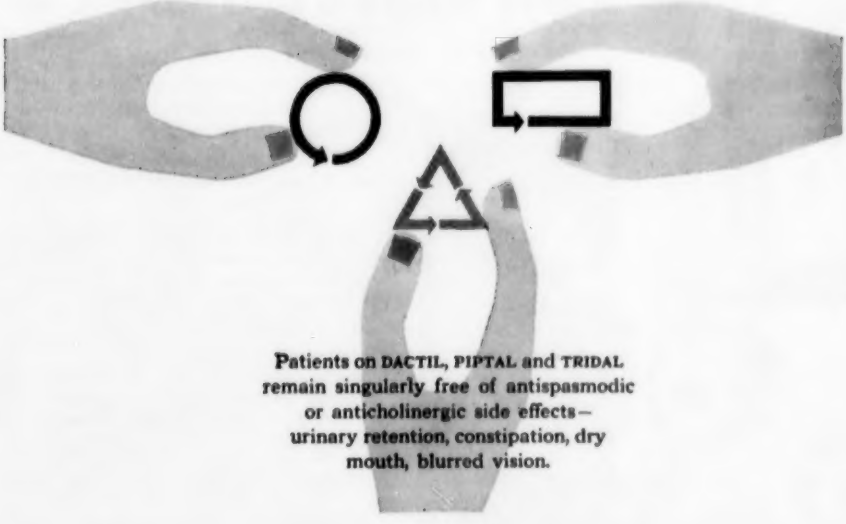

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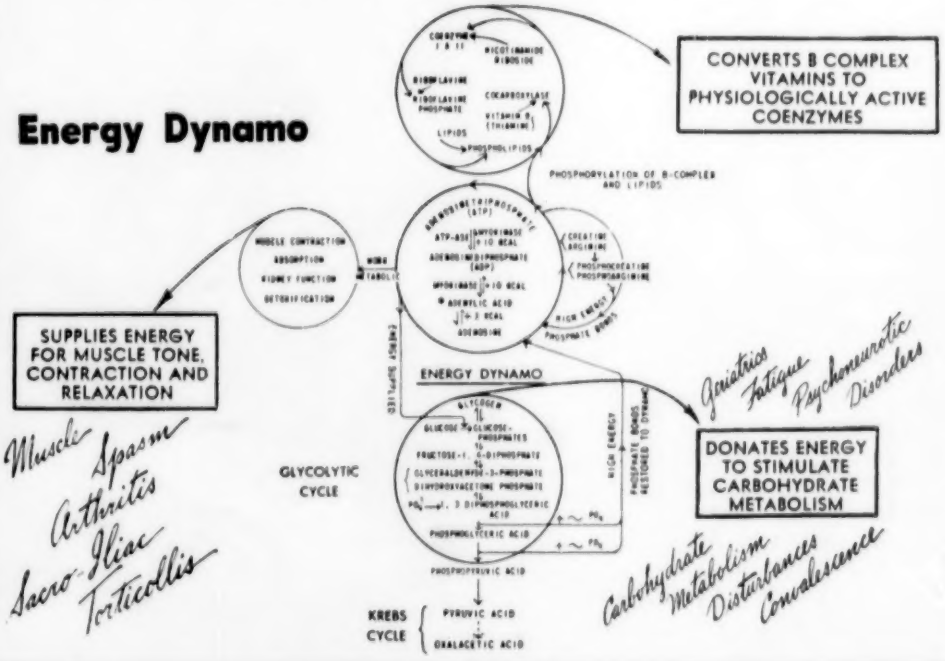

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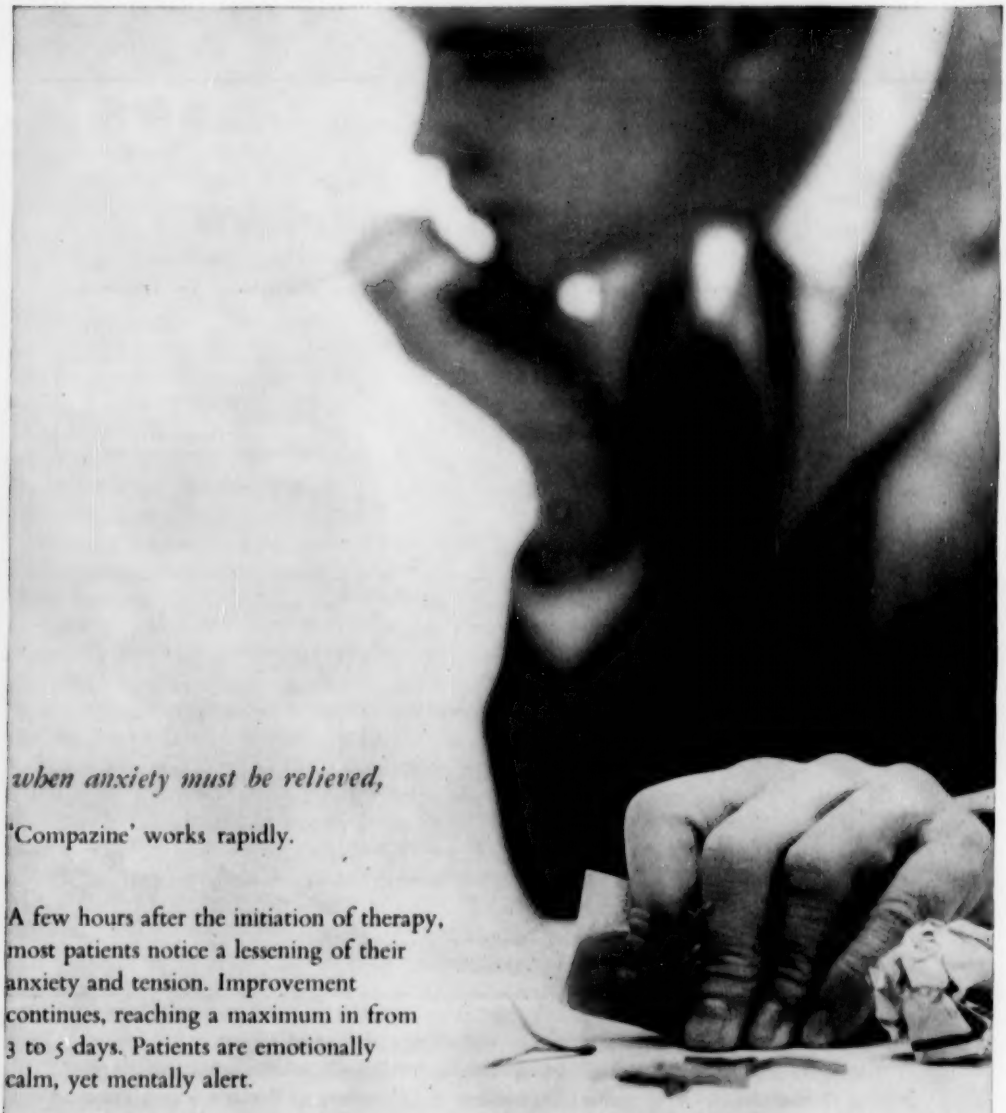

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INTERNATIONAL RECORD OF MEDICINE

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The Hippocratic Oath

Douglas Guthrie, M.D., F.R.C.S.
EDINBURGH, SCOTLAND

In the hall of the Mayo Foundation House at Rochester, Minnesota, formerly the home of Dr. Will Mayo and now serving as "a meeting-place where men of medicine may exchange ideas for the good of mankind," there is a stained-glass window that commemorates the progress of medicine, down the ages, along the three parallel lines of education, practice, and research. One of the central panels represents Lister at work, and it bears the motto: "To cure sometimes, to relieve often, to comfort always."

THE HIPPOCRATIC IDEAL

Cure and relief may be brought to the patient by science, but comfort is the work of an art that lies outside the fields of physical diagnosis and mass treatment. The science of medicine is today so powerful and efficient that there seems to be less actual need for the art, which, in consequence, is likely to be neglected. Our "journals of medicine" are now "journals of medical science," from which art has disappeared. With the advent too of nationalization and specialization, medical practice has become less intimate and less personal. Never before, perhaps, has there been greater necessity for closer attention to the ideals embodied in the Hippocratic Oath, that great code which magnifies the art of medicine, and which, in various versions, has guided the conduct of each successive generation of practitioners during many centuries.

OTHER ETHICAL CHARTERS

Long before the time of Hippocrates the practice of healing was regulated by laws and rules. No doubt prehistoric man, like primitive man as existing today, followed such regulations. Perhaps the earliest known code is that of Hammurabi (about 2250 B.C.), engraved on a pillar of hard stone and still on view in the Louvre. This code was, in fact, a law, with statements of medical fees—10 talents of silver to the

---

This paper is an abridged version of chapter XIV of a recent work, entitled *Medical Ethics*, edited by Dr. Maurice Davidson and published by Messrs. Lloyd-Luke (Medical Books), Ltd., London, by whose kind permission it is here reproduced.

physician who successfully opened an abscess of the eye, but two talents if the patient was a slave. On the other hand, there were severe penalties; for example, if the sight of the eye was lost or if the victim died, the hands of the surgeon were to be cut off. If the patient happened to be a slave, the surgeon was simply to supply another slave in his place. There is no mention of any penalties in the Hippocratic Oath, which is a set of ideals rather than a law.

Other codes of conduct and of bearing, framed after the time of Hippocrates, include that of the Indian surgeon Susruta who, early in the Christian era, made rules for the selection of medical students or pupils, who were to be chosen for "a noble countenance, a cheerful spirit, and a readiness to endure pain and weariness."

Not until about A.D. 1230 do we find definite regulations for medical education. It was then that the enlightened monarch, Frederick II, decreed that the medical course should be preceded by three years' study of logic and that no one might practice medicine without having passed the examination of the School of Salerno.

Still later, at the beginning of the fourteenth century, we find Lanfranc, of Milan and Paris, advising the physician "to be true and humble, to speak no ribaldry, to avoid any self-praise, and to help poor men without reward."

The ethical code of Maimonides (A.D. 1135–1204) is often placed alongside that of Hippocrates. Born of a well-known Jewish family in the city of Córdoba, Maimonides practiced there and later in Cairo, where he became physician to Saladin the first Sultan of Egypt. In his philosophy Maimonides attempted to reconcile Jewish and Moslem beliefs. His best known work is his *Guide to the Perplexed*. The *Prayer of a Physician*, ascribed to him, commences thus: "Endow me with strength of heart and mind so that both may be ever ready to serve the rich and poor, the good and wicked, friend and enemy,—and may I never see in the patient anything else but a fellow creature in pain."

HIPPOCRATES AND HIS DOCTRINE

By far the most significant of the codes of medical conduct was, and still is, the Oath of Hippocrates, which has outlived all other similar documents.

The discovery of a principle is always more significant than the discovery of a fact, and the first statement of those ethical principles that regulate the practice of medicine was surely a discovery of the first importance, for which Hippocrates well deserves his title of Father of Medicine. We need not pause to argue whether Hippocrates existed at all, whether there were three physicians bearing that name, and whether the Hippocratic works were written by a school, or team, of physicians. It is simpler and more practical to believe, as most of us do, that Hippocrates was born on the Isle of Cos about 460 B.C., that he taught and practiced there and elsewhere in Greece, that it was he who separated medicine from magic, stating that no disease was sacred, but that all diseases arose from natural causes, and that nature was the chief healer, the *vis medicatrix naturae*. Hippocrates was a shrewd and exact observer who used his unaided senses with excellent effect. He also emphasized the value of prognosis, or foreknowledge, and all his writings are still worthy of study. Among the best known of his writings is *The Oath*, a simple and straightforward charter of medical ethics or conduct.

DATES AND EDITIONS OF THE OATH

Authorities are by no means agreed regarding the original date of the Oath usually associated with the name of Hippocrates. Edelstein states that it was introduced by Pythagoras about 500 B.C., while Singer thinks that it may not have appeared until Roman times. Many manuscripts are extant; one of the earliest, dating from the tenth century and bearing the name of Urbinas, is preserved in the Vatican Library. The best manuscripts, tenth to fourteenth century, are listed by W. H. S. Jones in his indispensable work, *The Doctors' Oath* (Cambridge, 1924). The first Latin edition to appear in print is dated, from Rome, 1525; the earliest Greek printed edition was issued a year later. Four English versions of the sixteenth century, by Securis, Newton, Read, and Lowe, have been described by S. V. Larkey.[1]

In the original version of the Oath there is no mention of free treatment for the poor, but in Thomas Newton's work, *The Old Man's Dietarie* (1586), the Oath, which forms part of this book, includes the promise "that I shall not be squeamish to bestow my skill upon the poor and needy, freely and without fee." Although he did not mention it in *The Oath*, Hippocrates, in *Precepts*, advised his followers "not to be too unkind, but to consider carefully the patient's means . . . and sometimes give your services for nothing." The Oath included by Maister Peter Lowe in his textbook *The Whole Art of Chirurgerie* (1597), contains the following phrase, "I shall patiently sustain the injuries, reproaches, and loathsomeness of sick men, and all other base railings," thus suggesting that every doctor should cultivate the virtues of equanimity and self-mastery, so highly praised by Sir William Osler in his splendid essay, *Aequanimitas* (1889).

The excellent French translation by Littré was published in 1839, and in 1849 there appeared the English version by Francis Adams, the general practitioner of Banchory, Deeside, who translated many Greek medical classics. Later English renderings are by W. H. C. Jones (Loeb Library), 1923, and by John Chadwick and W. H. Mann, 1950.

It need hardly be added that the Oath is not the only Hippocratic work relating to ethics. Scattered throughout his works are many wise ethical counsels. An oft-quoted phrase, which goes to the root of the matter, states that "Where the love of man is, there is also love of the Art." The Oath is a charter or ideal, and not in any sense a law. No penalties are mentioned; it is an appeal and not a threat.

THE CHRISTIAN VERSION

There have been many renderings and many interpretations of the Hippocratic Oath. The first important digression from the original was the Oath as adopted by the early Christian Church, of which the best known manuscript is that of Urbinas in the Vatican Library of tenth century date. The Christian Oath is modified, "so that a Christian may follow it"; there is no mention of "swearing" the Oath. It is written in the form of a cross.

The first important difference is the omission of any reference to pagan deities. The initial invocation is not "I swear," etc., but is a beatitude: "Blessed be God the Father of our Lord Jesus Christ who is blessed for ever and ever; I lie not."

There is no praise of the teacher, nor any preferential treatment of him or of his sons or other pupils. Obviously the early Christian Church discouraged all secret societies and trade unions. Christian benevolence should be universal, and an exclusive circle of practitioners could not be permitted by those who held all men as brothers.

Another feature of the Christian Oath is the absence of the clause that prohibits surgery, or at least lithotomy. It was natural, perhaps, that the early Christians, who attributed healing power to God alone, should disapprove of operative interference, just as they discountenanced dissection of the human body.

MEDICAL ETHICS OF EIGHTEENTH AND NINETEENTH CENTURIES

Before dealing with the administration of the Hippocratic Oath, let us glance at the development of medical ethics in comparatively recent times. The term "medical ethics" came into general use after Thomas Percival of Manchester (b. 1740) published, in 1803, his well-known treatise bearing that title.

This book was an advance on the earlier work of Professor John Gregory of Edinburgh, the father of James Gregory of powder fame. Gregory's six lectures, entitled *The Duties and Qualifications of the Physician*, printed in 1772, reaffirmed the dignity of the medical profession, or rather of the physician, who had been the victim of many a satire since the days of Molière. This work dealt with medical etiquette, or the personal qualities of the physician, and his duty to his colleagues.

Percival's treatise took a wider view. It was called *Medical Ethics*,[2] not merely etiquette, although it did lay stress on a good bedside manner, as was the custom of the time. Percival was a man of distinction, had studied at Edinburgh and graduated M.D. at Leyden in 1765, an F.R.S., and was the friend of Voltaire, Franklin, Hunter, and others. Percival had already made important contributions to sociology before he wrote the book for which he is chiefly remembered. His interest in ethics arose from the difficulty of staffing the Manchester Infirmary during a typhoid epidemic, and he set himself to enunciate a code of precepts for the professional conduct of physicians and surgeons. The book met with much criticism, but it led to the better conduct of practice and it was highly regarded by the newly founded medical schools in the United States, as was also the work of Gregory. Percival's is one of the most interesting of medical classics; it has formed the basis of all subsequent work on the subject.

A treatise entitled *The Young Practitioner*, by J. de Styrap, Physician to Salop Infirmary, dated 1890, is a guide to medical etiquette rather than medical ethics. The newly qualified physician, just starting practice, is advised to purchase a good-looking horse and to write his prescriptions in clear and legible Latin.

The eminent American neurologist, Silas Weir Mitchell, covers much the same ground in his *Doctor and Patient*, published in 1888. Another book, which was highly regarded during the early years of the present century, was Robert Saunby's *Medical Ethics, a guide to professional conduct*, dated, from Bristol, 1902.

A more modern view was adopted by W. G. Aitchison Robertson, who gave good

counsel for his time in a work entitled *Medical Conduct and Practice* (1921). Those, and other works of similar nature, while they give an interesting picture of the state of medical practice, have been rendered obsolete and redundant by the profound changes that have taken place in the practice of medicine during recent years. A book still well worth reading, containing much wise advice applicable even today, is *The Physician's Art*, by A. G. Gibson of Oxford (1933). It is "an attempt to expand the fragmentary work written in 1669 by John Locke, the philosopher and physician, entitled *De Arte Medica*," which is reprinted as the first chapter of Gibson's scholarly work.

During the past two decades the ethical basis of medical practice has altered vastly and an entire revaluation of medical ethics, such as the present work provides, is much to be desired. The Oath of Hippocrates should ever be regarded as the ideal to be followed, although, of course, it requires modification to bring it into line with current thought and practice. In 1953 the British Medical Association rendered a useful service by publishing a 20 page booklet on *Ethics and Members of the Medical Profession*, which contains all the information likely to be required by the practitioner.

THE ADMINISTRATION OF THE OATH

It must be clearly understood that the Oath was devised not as a law but as a precept. Unlike the Code of Hammurabi, it makes no mention of penalties. The Hippocratic Oath was a counsel of perfection; an attempt to set up a high moral standard. For centuries, and indeed until the establishment of such courts as the General Medical Council, founded in 1858, an appeal to conscience was the only means of elevating the moral tone of the medical profession, and of showing that character was as important as knowledge in the practice of medicine. Whether the Oath was actually "administered" in early times is a matter of controversy.

When medical schools and universities were established, it was natural that some form of promise should be given by those who were about to graduate. As already mentioned, the School of Salerno adopted the rules made by Frederick II about A.D. 1230, although those rules concerned the period of study and standard of examination, rather than the conduct of the physician. One of the earliest bodies to adopt the Hippocratic Oath as a form of promise on graduating in medicine was the University of Montpellier (1181). The graduand repeated the words: "I promise and swear, in the name of the supreme Being, in the presence of the masters of this school and of my dear fellow-students, and before the image of Hippocrates, to be faithful to the laws of man and of honour in the exercise of medicine." He further promised to attend the poor without fee, to maintain silence when entrusted with secrets, to maintain a high moral standard, and to pass on to his children the knowledge imparted by the masters. The University of Vienna, founded in 1365, requires of its graduates that they shall "hold ever sacred the name of this University," shall cultivate and increase knowledge and use it "for the well-being and prosperity of man," and "perform all the duties befitting an upright physician, with that humanity which is meet and proper." The graduand of the University of Basel, founded in 1460, promises to "hold the investiture this day in the light of a sacred

ordinance," also "never to use quack nostrums or harmful drugs," and "to undertake the tasks of your profession with becoming piety." Those, and other early universities, continue the practice to this day, and it is only right and proper that every medical school should follow their example.

I have recently tried to ascertain the extent to which the Hippocratic Oath is adopted in some academic circles, and the results of the inquiry are rather surprising. In South Africa (University of Cape Town), candidates, before being admitted to the qualifying degree, must sign a declaration stating that they "will exercise their profession for the good of all persons in their care, will hold in due regard the honourable traditions of the profession, and will be loyal to the University and endeavour to promote its welfare." In Canada the use of the Hippocratic Oath is almost universal. At the University of Western Ontario medical graduates recite the Oath in unison in addition to signing it. At the French University of Montreal it is read out by one of the graduates, and subscribed by all.

The Royal Colleges of Physicians and of Surgeons, in England, Scotland, and Ireland, demand of their Licentiates and Fellows a promise to promote the reputation and Dignity of the College and to be obedient to the Laws, but there is no reference to the Hippocratic Oath.

At Oxford University there is no administration of the Hippocratic Oath to medical graduands, although, as students, they may see the version prominently displayed in the Radcliffe Library. Liverpool University prints the Oath of Hippocrates in the Calendar, so that students "may read it with profit," but it is not administered or signed at graduation ceremonies.

At the University of Edinburgh, since 1947, the graduands all stand at the graduation ceremony while the Dean reads to them the Declaration, to which they assent by raising their right hands. The procedure at the University of Glasgow is very similar to that at Edinburgh, but the administration of the Oath is conducted by the Dean at a private ceremony before the graduation ceremony.

Perhaps it would be a good idea if all universities would combine in formulating a clearly worded declaration, based on the Hippocratic Oath, which would be generally acceptable. It would be for the good of the medical profession if the universities were to take more account of the great code of conduct that, in one form or another, has been adopted by many generations of physicians and has profoundly influenced the practice of medicine since the days of Hippocrates. Medicine demands character as well as knowledge. Today it is more essential and desirable than ever that medicine should remain a vocation and a profession, rather than a technique or a business, and should, in fact, remain "The Art," as Hippocrates called it. The maintenance of a high ethical standard would be greatly assisted if every medical graduand, at a solemn ceremony, were to dedicate himself to his calling by publicly adopting those principles that for centuries have guided the healing art toward its highest destinies.

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How Hippocrates Made His Diagnoses*

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For many centuries, Hippocrates has been called the Father of Medicine. This great Greek physician, who lived more than 2000 years ago, has been placed by his fellow physicians upon a pinnacle of eminence never attained by any physician before or since. His contemporary, the philosopher Plato, wrote and spoke of him in terms of the highest praise, and this praise and veneration have continued from generation to generation. Thomas Sydenham, the great English physician, was called the English Hippocrates; Casál was referred to as the Spanish Hippocrates; and Boerhaave's enthusiastic admirers climaxed their praise with the appellation the Dutch Hippocrates. In the Middle Ages, the great medical school and hospital of Salerno called itself the *Civitas Hippocratica* (the city of Hippocrates). As other medical schools were founded and grew to eminence, they in turn called themselves *Civitas Hippocratica*.

What was the reason for this extraordinary veneration, approaching at times a veritable worship of Hippocrates? Was Hippocrates a legendary person, a myth like Hercules, the story of whose exploits grew with each succeeding generation of Greeks until he became a divinity?

Debunkers, contrary to popular impression, are not a modern phenomenon. They began early in the nineteenth century to assert that Hippocrates was a mythical person and that the stories of his medical skill were only a legend, like the legends of Zeus or of Asklepios. It is very easy to refute such stories. The best proof of the existence of a man is the testimony of his contemporaries. Plato, Aristotle, and Aristophanes refer to Hippocrates—Plato and Aristotle describe him as a great physician; Aristophanes recalls him as the author of the Hippocratic Oath.

Hippocrates lived in the Golden Age of Greece. His contemporaries were Pericles, the statesman; the philosophers Socrates, Plato, Aristotle, Xenophon, and Protagoras; the dramatists Aeschylus, Sophocles, Euripides, and Aristophanes; the poet Pindar; the historians Herodotus and Thucydides; the sculptors Phidias, Praxiteles, and Polygnotus. No nation in human history can boast of such a galaxy of imperishable names as Greece had during the Golden Age, the Age of Pericles. Medicine, to our pride, was represented by a man as eminent in his field as the great philosophers, poets, dramatists, historians, and sculptors whose names I have mentioned.

In the tenth and eleventh centuries B.C., the ancient Greeks, following the advice of the Oracle of Delphi, migrated to the East and settled on a chain of islands and on the mainland of Asia Minor, which the Greeks called Ionia. These islands and the mainland gave Greece some of her most illustrious sons: the philosophers Thales, Pythagoras, and Xenophon; the poets Anacreon, Theocritus, and Herondas; the geographer Strabo; Apelles, the greatest artist of antiquity; Herodotus, the Father

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of History; and Hippocrates, who was born on the little Island of Cos, an island only 25 miles in length and six miles in width at its widest point. Here he was educated, practiced medicine, taught his pupils, discussed cases with his colleagues, founded the Hippocratic or Coan school of medicine, and composed, with his pupils and associates, what we call today the Hippocratic Corpus or Collection, which has come down to us and has been translated into English, French, and German, the most notable translation being that of Littré, a French physician, who was also a classical philologist. His translation is in 10 volumes. This translation occupied Littré for more than 30 years, the first volume appearing in 1839, the last in 1861. From these works we can obtain a clear idea of what Hippocrates believed, what he taught, and how he practiced medicine.

All primitive peoples believe in the demoniac theory of disease—the Indians in our own country, the Babylonians, the Hebrews, the Egyptians, the Romans, and the ancient Greeks were no exception. The belief was widespread among the Greeks that the gods sent diseases down upon men. Hippocrates denied this repeatedly and asserted that the gods do not send diseases down upon men but that men bring diseases upon themselves. "Those who refer disease to the gods," he says in a vigorous attack on this idea, "appear to me to have been just such persons as the conjurers, purificators, mountebanks and charlatans now are, who give themselves out for being excessively religious, and as knowing more than other people."

Hippocrates had some fundamental ideas regarding disease and its causation that have, 2000 years later, a very modern ring. While most Greek writers used the word, παθος, or suffering, for disease, Hippocrates often employed the term, πονος, or struggle. He described health as the state in which the humors of the body were all harmoniously balanced in their proper proportions—endocrine balance, we should probably say today. When the body is attacked, its defense mechanisms react and attempt to restore the equilibrium. What we call disease is really a struggle of the body to regain its equilibrium. In recent years, we have heard much of the role of stress and the body's reaction to stress as a cause of disease. The idea is not new but stems back to Hippocrates. Hippocrates was much interested in fever, often the most marked sign of this struggle the body was making to regain its equilibrium. He states that in some diseases, fever seems to have a curative effect, mentioning specifically spasms, tetanus, and strangury. However, Hippocrates has fame enough without being called the father of fever therapy. Hippocrates had many original and at the time revolutionary concepts of disease, which have been studied and commented on by many eminent physicians throughout the centuries. During the Middle Ages and even into the Renaissance, no physician considered himself learned or was so considered by his colleagues until he had written a commentary on Hippocrates. But it was not his theory of health and of disease that brought students to Cos, where, according to tradition, Hippocrates sat under the old plane tree demonstrating his patients to his students and colleagues, diagnosing the diseases, and prescribing treatment. This brings us to the central theme of this talk—"How did Hippocrates make his diagnoses?" Fortunately we are spared the pitfalls of speculation, for Hippocrates left us descriptions of 42 clinical cases, almost the only records of the kind for the next 1700 years!

The first procedure was to take the patient's history. After recording the patient's name, race, age, place of dwelling, occupation, Hippocrates asked questions about the locality in which the patient was living and the season of the year during which the illness began. Hippocrates had traveled widely, and during his travels, he had studied the effect of climate on the physique and the health of various races, the effects of different diets, of different types of water on peoples. In certain areas, he found bladder stones very common and blamed them on the water the people drank. Certain diseases he found most prevalent in winter, or in spring, or in summer, and he found also that recovery depended in part on the season of the year. All these observations he recorded in his treatise, *On Airs, Waters, and Places*, the first comprehensive treatise on medical geography, climatology, and anthropology.

Hippocrates also inquired carefully into the habits of people, whether they drank too much wine and what they ate. On one occasion in Ainos (Enos), he encountered an epidemic of paralysis, or, as he expressed it, "impotence of the legs." On careful inquiry he found that the victims had been eating large quantities of chick-peas. This is the first account of lathyrism, which, centuries later, was seen in India and in Algiers, a degeneration of the lateral spinal tracts caused by two toxic alkaloids in the chick-pea, producing first spasticity of the legs and then complete paraplegia.

Hippocrates also inquired carefully into the family history. He stressed the role of heredity in many diseases, in tuberculosis, in asthma, in epilepsy. In describing

Tree of Hippocrates on the Isle of Cos.

the illness of the daughter of Euryanax, who suffered from a perirectal abscess, he remarked, "She showed signs of an inherited tendency to consumption."

Having completed the history, Hippocrates began his physical examination of the patient, first employing inspection. A verbatim account emphasizes how keen and acute were his powers of observation:

> The master of a large ship mashed the index finger of his right hand with the anchor. Seven days later a somewhat foul discharge appeared; then trouble with his tongue—he complained he could not speak properly. The presence of tetanus was diagnosed, his jaws became pressed together, his teeth were locked, then symptoms appeared in his neck: on the third day opisthotonus appeared with sweating. Six days after the diagnosis was made he died.

This terse dramatic picture of tetanus is not excelled, even in our modern textbooks.

Again:

> He would observe thus in acute diseases: first, the countenance of the patient, if it be like those of persons in health, and more so, if like itself, for this is the best of all; thereas the the most opposite to it is the worst, such as the following: a sharp nose, hollow eyes, collapsed temples; the ears cold, contracted, and their lobes turned out; the skin about the forehead being rough, distended, and parched; the color of the whole face being green, black, livid, or lead-colored.

This is the famous description of the Hippocratic facies.

Another example of Hippocrates' powers of observation:

> The vertebrae of the spine when contracted into a hump behind from disease, for the most part cannot be remedied, more especially when the gibbosity is above the attachment of the diaphragm to the spine. . . . And when the gibbosity occurs in youth before the body has attained its full growth, in these cases the body does not usually grow along the spine, but the legs and the arms are fully developed, whilst the parts (about the back) are arrested in their development. . . . Such persons appear to have more prominent necks than persons in good health, and they generally have hard and unconcocted tubercles in the lungs. . . . When the gibbosity is below the diaphragm, in some of these cases nephritic diseases and affections of the bladder supervene, and abscesses of a chronic nature, and difficult to cure, occur in the loins and groins, and neither of these carries off the gibbosity.

Here is a perfect description of Pott's disease 2000 years before Pott was born and, what is more interesting, a mention of a cold abscess and of the associated tubercles in the lung. Franciscus Sylvius (1614–1672) is usually described as the discoverer of tubercles in the lungs. A literal translation of the Greek here is "hard and undigested (cheesy) nodules in the lungs." This account also suggests strongly that Hippocrates may have performed post-mortem examinations. If so, his example was not followed for a century until Herophilus appeared in Alexandria.

Another observation: "Philiscus, who lived by the Wall, took to bed on the first day of acute fever. . . . The respiration throughout, like that of a person recollecting himself, was rare and large." This is probably the first description of Cheyne-Stokes respiration, made known to the medical world by John Cheyne (1818) and William Stokes (1846). The description of the respiration "like that of a person

Antique statue of Hippocrates found on the Isle of Cos.

recollecting himself" is extremely apt. The patient forgets to breathe and then suddenly recollecting begins to breathe again.

Hippocrates was familiar with the following phenomenon: "Paralysis appears on the left side, when injury to the head is on the right side, in contrast the paralysis is rightsided when the injury is on the left side." This observation is often ascribed to Paracelsus.

Hippocrates was a careful student of tuberculosis and has left us remarkable pictures of this disease in its various stages. The appearance that characterizes consumptives, he wrote, "is a smoothness of the skin, slight pallor, freckles, a slight flush, sparkling eyes, white sputum, and winging of the shoulder blades." This is the first mention of the winged or alar scapulae, stressed by every teacher of physical diagnosis since the days of Hippocrates.

He saw and described many cases of empyema. He noted, "They bring up no sputum worth mentioning, they sweat about the neck and shoulders, their eyes become sunken, the cheeks flushed, the tips of the fingers become warm and rough, and the nails become curved." Here is the description of the Hippocratic fingers or clubbed fingers, known to every medical student the past 2000 years.

After inspection, Hippocrates proceeded, just as we have done since, to palpation. On one occasion, Hippocrates seemed to have felt called on to defend this procedure when he wrote, "One who palpates the body and the pulse makes fewer mistakes than one who does not palpate." He stressed particularly palpation of the ab-

domen, pointed out that the abdomen in health was soft and palpation produced no pain while, in certain acute states, the wall of the abdomen was hard and pressure produced severe pain.

Laënnec, the discoverer of auscultation, says, "Hippocrate avait tenté l'auscultation médiate" (Hippocrates attempted mediate auscultation). He called attention to a passage neglected by all commentators throughout the ages. This he had read but forgotten until his investigations caused him to go back and read anew the famous passage:

> If hydrops of the lungs forms, the patient has fever and a cough; respiration is rapid; the feet swell; all the nails are drawn together and he feels all the complications of empyema only with less force and more slowly. If you introduce an infusion into the lung or administer a still bath or fumigate, the pus does not appear; by that you recognize that it is not pus but water; and, if applying your ear against the chest, you listen for some time, it boils within like vinegar.

Hippocrates, with his ear against the chest, obviously heard bubbling râles.

Another interesting observation on auscultation is found further in the same book:

> When the lung falls against the ribs, the patient has a cough and orthopnea; the expectoration is colorless; he feels pain in the chest and over the back; the lung is extended pressing on the side; it feels to the patient as if he had a weight on his chest; acute pains prick him; a sound like that of leather is heard.

Here is a clear description of a pleural friction. A later sentence in this same paragraph arrests our attention: "If this affection follows a wound or an incision for empyema (this happens occasionally), one should attach a cannula to a bladder, and filling the bladder with air, one should force the air into the interior." This passage escaped the eyes of most of his numerous commentators. Gardeil in 1801, commenting on this passage, remarked,

> If I understand the text of Hippocrates which is here very perplexing, it describes a procedure apparently long forgotten of which I do not see the idea. The bladder filled with air does not appear to me to have been introduced with any other view than hindering adhesions of the lung with the pleura.

It is certainly no poetic license on the part of Baisette to see in this procedure an early application of therapeutic pneumothorax, introduced by Forlanini in 1895.

The famous Hippocratic succussion is described by the master in a few words: "Prepare a warm bath, set him upon a stool, which is not wobbly, someone should hold his hands, then shake him by the shoulder and listen to see on which side a noise is heard." Nothing could be more simply or more accurately told.

"The nose," Hippocrates wrote, "often gives us valuable clues in fevers, for the odors are very different." We of the present era seem to have suffered some diminution in our acuteness of smell, which previous generations of physicians stressed as important. While all of us are familiar with the acetone breath in diabetic acidosis and the fetid nauseating breath in abscess of the lung, yet many physicians of the present generation have forgotten that certain diseases emit distinctive odors—

the mousy odor in typhus fever, the sweetish fetid odor of measles, the acid sweaty smell of rheumatic fever, and the characteristic odors, difficult to describe, of diphtheria and of smallpox.

Hippocrates, after completing his physical examination, examined the excreta—the sputum, stools, and urine. He described bloody sputum and rusty sputum in pneumonia, foul sputum in empyema, frothy sputum, always drawing the correct diagnostic inferences. He examined the stools with care, was disturbed at the presence of blood and pus, and frequently cleared up the problem of the patient's abdominal distress by demonstrating roundworms in the stools. The urine he always examined with meticulous care. He warned his students that complete suppression of urine was often followed by unconsciousness and convulsions—an early description of uremia. Urine containing gravel often foretold the formation of kidney or bladder stones. Bloody urine or purulent urine indicated lesions or infections of the urinary tract. In one of his aphorisms, Hippocrates wrote, "When bubbles settle on the surface of the urine, they indicate disease of the kidneys, and that the complaint will be protracted."

Francis Adams, whose English translation of Hippocrates, first published in 1849, remains one of the best of all translations, commenting on this passage, noted, "It can scarcely admit of a doubt that our author here refers to *albuminous* urine, which it is well known is also *frothy*, and is now generally admitted to be connected with disease of the kidneys."

It must have been a marvelous experience to have sat under the branches of the old plane tree on the Isle of Cos, listening to Hippocrates as he demonstrated his patients, and following the working of a master mind. Today, it may not seem remarkable that Hippocrates, in making a diagnosis, took the patient's history, inquired carefully about his present illness, his past history, his family history, his habits, his work, where he lived, what he ate and drank, and then made a careful physical examination, employing inspection, palpation, and auscultation, following this with a careful examination of sputum, urine, and stools. But in Hippocrates' day, soothsayers, astrologers, and the priests of various cults often dominated medical practice. They made their diagnoses by studying the stars, by examining the organs of sacrificial animals, by interpreting dreams, by studying omens and portents. This makes the achievement of Hippocrates stand out in bold and dramatic relief.

Hippocrates created a new epoch in medicine and left an enduring impress on medicine, undimmed by the passage of 2000 years. We today still practice Hippocratic medicine. The methods he introduced have been refined and extended with the passage of time, but the underlying principles, the methods and manner of procedure, the high ethical precepts he advocated are ageless and timeless. We are still proud to be the disciples of Hippocrates and to call him the Father of Medicine.

Pharmaceutical Research

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The annual reports of the leading pharmaceutical companies of the United States offer some interesting and exciting information as to the trends of research in which these companies are engaged. Many lines of investigation are still no doubt in the secret stage. Some of the research points toward definitely new products, some to modifications of existent products, and much to the development of combinations for which special claims are made.

In a recent editorial on pharmaceutical research, the *British Medical Journal* (May 11, 1957) suggested that Great Britain is behindhand in pharmaceutical research. The editorial points out that reserpine was isolated in Switzerland, chlorpromazine synthesized in France, from Germany came analgesics like pethidine and methadone, drugs for schistosomiasis, and the new sulfonamides for the oral treatment of diabetes. The United States is thanked for cortisone, ACTH, the Salk vaccine, and an oral ganglion-blocking product.

The *British Medical Journal* emphasizes the work of American pharmaceutical industries for which research is a main business since the largest profits are associated with the introduction of new drugs. The British firms rely on the sale of established remedies or well-known substances with proprietary names. The *British Medical Journal* points out that salaries for investigators who work for American pharmaceutical industries run from $25,000 to $65,000 a year and that even a young man who has recently taken his Ph.D. degree will earn from $6,000 to $8,000 a year. In Great Britain industrial positions pay little, if anything, more than university posts. Even when the salary is high "the Inland Revenue takes the bulk of it." The *British Medical Journal* suggests that more useful as distinct from academic research be done in the universities thus offering perhaps some advance on current conditions.

In an address on "Planning of Research by Pharmaceutical Companies," T. F. Davies Haines, president of Ciba Pharmaceutical Products, Inc., discusses the research budgets of American pharmaceutical companies and finds that the mean for 11 leading companies was 4.8 per cent of sales, with one company reaching 10.7 per cent in one year. Of 17 chemical companies listed on the New York Stock Exchange, the largest spender reached 5.3 per cent of sales, and the mean was 2.8 per cent. One pharmaceutical company spent 33.7 per cent of its net profits before taxes on research. As a result, this company's sales tripled over a five year period. The mean expenditure for research was 21.1 per cent of net profit.

The biggest problem in this field today is the securing of competent personnel. While tremendous advances have been made, indications are certain that still greater advances await investigators in the near future.

ABBOTT LABORATORIES

The research results reported by Abbott begin with a unique new product in the

ataractic class now in the final stage of clinical investigation. The product, called Harmonyl, is a new alkaloid of *Rauwolfia canescens*. The product is said to be indicated especially for persons with mild anxiety symptoms but also for institutionalized mental patients. Investigators report that it reduces the blood pressure in mild essential hypertension.

The products developed by Abbott for the control of epilepsy are supplemented by a new compound for grand mal epilepsy and an anticonvulsant, Peganone. Reports are that Peganone controlled convulsions with almost complete absence of serious side effects in 65 per cent of epileptic patients whose convulsions were not controlled by existing products. The present list of Abbott products for control of epilepsy includes Paradione and Tridione for petit mal, Phenurone for psychomotor seizures, and now Peganone for grand mal.

AMERICAN CYANAMID COMPANY

The Lederle Laboratories Division, which is the medical company of the American Cyanamid Company, reports that research has developed an improved formulation of Achromycin tetracycline that is absorbed more rapidly into the blood stream and gives higher blood levels for a longer period. This product is to be marketed as Achromycin V.

A new long-acting sulfa product called Kynex is expected to be released for general use by physicians shortly.

A new steroid compound, triamcinoline, is said to possess anti-inflammatory and metabolic properties superior to other similar products now available.

This company is especially concerned with the development of a modified live virus vaccine against infantile paralysis. The research on this product is reported from time to time but no product of this type is as yet available for general use.

AMERICAN HOME PRODUCTS CORPORATION

The substantial increase in sales of the American Home Products Corporation included particularly ataractic drugs. This corporation controls also the products of Ayerst Laboratories, including Premarin and a variety of preparations for administration to aging patients that are believed to have the virtue of delaying the onset of degenerative changes. The company also has an anticonvulsant, Mysoline.

New products released in 1956 included Thiosulfil-A, used in the treatment of urinary tract infections; a preparation of ferrous sulfate with vitamin C; and a multiple vitamin preparation in a candy-flavored base.

Another division, called Ives-Cameron, offered an analgesic relaxant named Synalgos and a substance, Monichol, designed to normalize cholesterol metabolism.

Wyeth Laboratories, another subsidiary of American Home Products, marketed Equanil and Sparine as ataraxics, Phenergan for preoperative sedation in surgery, and Ansolysen, used in the treatment of hypertension. This company produces several products of penicillin V, including combinations offered for general antibiotic uses and specifically for the prevention of bacterial complications in the common cold.

A new institute for medical research has been built at Radnor, Pennsylvania.

BURROUGHS WELLCOME & CO.

The Wellcome Physiological Research Laboratories were developed in 1894. Here were created the vaccines, serums, and antitoxins. In addition, veterinary immunology led to the establishment of the separate Wellcome Veterinary Research Station. Research in tropical diseases is carried on by Wellcome and its laboratories in Khartoum in the Sudan. In the United States the division called the Wellcome Research Laboratories is located in Tuckahoe, New York. These laboratories are engaged in developing an improved poliomyelitis vaccine. In antihistamine research the Wellcome Research Laboratories have contributed not only Perazil, which is chlorcyclizine hydrochloride, but also Marezine, which is offered particularly for seasickness, nausea, and vomiting. The company also produced Tricoloid, a brand of trycyclamol, which is an anticholinergic, and Procyclidine for release of the rigidity and tremor of parkinsonism. Among the antimalarials, the research laboratories developed Daraprim.

Investigation is now going on with 6-mercaptopurine designed for the treatment of leukemia. Other drugs in this area are Busulfan and Leukoran, which is a brand of chlorambucil, also used in leukemia. The laboratories are concerned with the development of relaxants and pressor drugs. The Wellcome Research Laboratories developed Polymyxin and, among anthelmintics, a piperazine citrate known as Antepar.

CIBA PHARMACEUTICAL PRODUCTS, INC.

The Ciba company is related to the Ciba company of Basle, Switzerland. This company has a long record of important contributions including such preparations as hormones, particularly cortisone and androstine. Ciba developed the new hormone Electrocortin, which is aldosterine. Widely known are such products as Nupercaine and Trasentine. The latter is a nonalkaloidal antispasmodic. Pyribenzamine and Privine are also widely known.

EATON LABORATORIES

The principal developments of the research laboratories of this company have included nitrofurans in a variety of forms, particularly a new type of dressing for treatment of burns. This is known as Furacin Soluble Dressing. It is used also in various infections of the skin and as a dressing following surgical procedures.

GEIGY PHARMACEUTICALS

Geigy Pharmaceuticals is a division of a Swiss company. Up to this year pharmaceutical research activities of Geigy have been primarily concerned with pharmacologic and clinical investigation of new compounds that were synthesized and found to be promising in the laboratories at Basle, Switzerland. This year plans have been completed for a basic pharmaceutical laboratory to be built in Ardsley, New York. The program in the United States is being planned to augment rather than overlap the research carried on in Europe. The basic pharmaceutical research in the

United States includes an extensive survey of promising antirheumatic drugs, compounds active on the central nervous system, analgesics, respiratory stimulants, radiopaque agents, anticoagulants, and chelates.

HOFFMANN-LA ROCHE, INC.

This company is also related to a company in Basle, Switzerland. Trends in the present research program include the following lines of investigation: hypertension, diseases of the circulatory system, arthritis, analgesia, stimulants of appetite, depressants of appetite, and ataractic drugs as well as drugs for control of cancer.

ELI LILLY AND COMPANY

In a recent address, Eugene N. Beesley, president of Eli Lilly and Company, stated that at present scientists of Eli Lilly are working on 55 different research projects covering most, if not all, of the major areas of medical interest, including cancer, cardiovascular diseases, and mental illness. The program is designed to discover new and improved medicinal agents and to manufacture products for independent investigators who cooperate with this company.

Outstanding new products include Cytellin (sitosterols, Lilly), a product for the control of excess cholesterol in the blood, and Tes-Tape, a simplified means for permitting diabetics to test their sugar level. Incidentally, during 1956 Eli Lilly made 70 per cent of all the poliomyelitis vaccine released by the National Institutes of Health.

MEAD JOHNSON & COMPANY

This company undertook an expanded research program beginning in 1952. During 1956, products development research produced 10 products, including Colace, which is for the management of constipation, a high calorie intravenous hydrolysate called Amigen 800, a new form of Pablum, which is a high protein cereal. As an indication of the trend of this work, studies are being made of 50 new experimental nutritional products; 14 experimental pharmaceutical products are undergoing clinical study although 50 are in process of development. A fermentation pilot plant has been constructed and an isotope tracer laboratory will be completed during 1957. A new toxicology laboratory was recently completed.

MERCK & CO., INC.

Among the products on which research is reported by Merck & Co. are Cathomycin, which is this company's brand of novobiocin. This product is known by other names, each of the manufacturers having a distinctive name for it.

Merck & Co. has also combined in a single tablet such products as Co-Deltra and Co-Hydeltra. Co-Deltra is a central core of the hormone prednisone within an outer tablet layer of antacids. Co-Hydeltra is similarly prednisolone with antacids. These tablets are designed to overcome the tendency to ulcer of the stomach, said to be a side effect of the use of prednisone. Another tablet, called Tempogen, is a multiple

compressed tablet containing a core of prednisolone and vitamin C with an outer layer of aspirin and antacid.

Inversine is Merck & Co.'s brand of mecamylamine, which is an antihypertensive agent—a ganglionic-blocking agent.

Another compressed tablet is Mephyton, which makes available in oral dosage form vitamin K_1 for the control of certain types of hemorrhage.

Interesting experimentation has also developed a product called Meprolone, which is a combination of prednisolone and meprobamate, better known as Miltown. This is offered as a muscle-relaxing agent for use particularly in rheumatic diseases.

A mental disease seen chiefly in infancy—oligophrenia—associated with excretion of phenylpyruvic acid, is apparently controllable by the use of a product called Ketonil, and this is said to be the first instance in which a mental disease has been identified and treated by dietary means.

Such developments are in accordance with the trend to study the biochemical aspects of disease and treatment directed to control of abnormalities that may be found.

WM. S. MERRELL COMPANY

Two pharmaceutical companies are subsidiaries of the Vick Chemical Company. They are the Wm. S. Merrell Company and the National Drug Company. The latter has begun construction of a two story addition to its research laboratory. New organic laboratories and a chemical reactor building are being developed at Merrell.

During 1956 the Merrell company added to its specialties Meratran with reserpine as an ataraxic; Frenquel, an antihallucinatory, anticonfusion drug particularly for use in schizophrenic hallucinations; an antitussive called Consol, which contains narcotine. This substance is said to be 6 times more effective than codeine.

OLIN MATHIESON CHEMICAL CORPORATION

E. R. Squibb & Sons, a division of Olin Mathieson Chemical Corporation, reports that its research includes cooperation with the National Cancer Research Program. A new radioisotope plant was developed at New Brunswick, New Jersey. Among recent developments of Squibb research are the antibiotic Mysteclin, Nydrazid for tuberculosis, Raudixin for hypertension, and curare products used in surgery. Among current research projects are studies of new agents for treating anxiety, such as ataraxics, investigations in synthesis of steroids, and continued screening of thousands of possible new antibiotics. Squibb laboratories also include a new building designed for manufacture of radioactive isotope pharmaceuticals. Radioactive gold, phosphorus, and iodine are already produced. Mention should be made also of the quest for new pesticides to combat insects, weeds, and plant diseases. Some 5000 such chemicals have been synthesized and 2000 have been screened.

PARKE, DAVIS & COMPANY

The annual report of Parke, Davis includes an announcement of the development

of a new medical research center, which will be on a 50 acre site near the University of Michigan campus in Ann Arbor, Michigan.

Parke, Davis & Company has applied to the Federal government for a license to market adenovirus vaccine for use in preventing virus infections of the nose, throat, and eye, a respiratory condition reported in several epidemics in recent years.

Parke, Davis announces also the development of a substance called DON (6-diazo-5-oxo-L-norleucine), which on the basis of experiments on laboratory animals is said to be many times more potent than the tumor-inhibitory antibiotic Azaserine, which was announced in 1954. While the new product has clearly demonstrated activity when used in animals, Parke, Davis is careful to say that there is no definite indication as of now that DON will be a practical product.

In the field of epilepsy a new drug Celontin is offered for psychomotor seizures and certain cases of petit mal epilepsy not properly controlled by other drugs. In this field Parke, Davis has Milontin, which is for petit mal epilepsy, and the widely known and used Dilantin for grand mal epilepsy.

CHAS. PFIZER & CO., INC.

The Pfizer company adopted in 1957 an unusual type of annual report directed to a wide public audience and already circulated as a special Sunday supplement with several leading newspapers.

The number of possible new antibiotics is now understood to be infinite. The Pfizer company announces the discovery of oleandomycin, especially effective against staphylococci and claimed to be synergistic with tetracycline. A compound of oleandomycin and tetracycline is now offered as Sigmamycin, and reports indicate that the compound is far more effective than either of the products given singly.

Another new product is Moderil (rescinnamine), a newly isolated component of the *Rauwolfia* root offered for the treatment of high blood pressure and emotional tension and said to be more free from side effects than other products in this field.

The Pfizer company continues its tremendous soil-screening program for antibiotics, its research on steroids, and particularly research in agricultural products involving antibiotics, vitamins, and hormones.

G. D. SEARLE & CO.

Nilevar is a new steroid drug developed by G. D. Searle & Co. "By its use the physician is able to increase the weight of the patient by building muscle and other non-fat tissues." With such metabolic changes the patient experiences an increase in appetite and some euphoria. Obviously such products are designed for those who cannot gain weight because of loss of appetite, such as occurs in chronic and debilitating illnesses, and also for patients who have not regained weight lost after surgery, and, finally, for encouraging growth in premature infants.

Rolicton is a product in the field of diuretics, a field in which this company has already developed the product called Mictine. Rolicton is offered particularly for ridding the body of edema fluid and has the advantage that the drug can be given orally.

Searle has just introduced a new synthetic abstergent under the name of Zanchol for the treatment of gall bladder conditions. A new ataraxic is being developed for severe mental disorders. A drug that may have a use in the field of physiologic birth control, to be strictly a prescription product available only through physicians, is probably to be marketed in the near future. The drug is said also to have virtue in various menstrual disorders.

SMITH, KLINE & FRENCH LABORATORIES

During 1956 five new specialties were developed by these laboratories, including a new synthetic hormone for the treatment of diminished metabolism called Cytomel, a long-term aspirin called Ecotrin, a liquid medication for administering sulfonamides called Sul-Spansion, and several forms of thorazine or chlorpromazine combined with Dexedrine.

THE UPJOHN COMPANY

Much of the research effort at The Upjohn Company in 1956 was concerned with the development of Orinase (tolbutamide), an oral antidiabetic agent. The pharmacologic testing previously reported had to be coordinated and extended. The release of Orinase in June 1957 was preceded by what was probably the most extensive clinical testing program in the history of pharmaceuticals.

Other projects covered almost all areas of medical importance, including nutritional, infectious, and cardiovascular diseases, cancer, and mental diseases. The most important categories of products studied were antibiotics, steroids, and nutritional agents. In the field of antibiotics, the company developed and released Albamycin (novobiocin) and Comycin (tetracycline phosphate complex with nystatin). Still in the research stage is Dalacin (streptovaricin), an antibiotic showing promise in the treatment of tuberculosis. Two new steroids were reported, Halotestin, an androgen that is now on the market, and Medrol, a synthetic adrenocortical steroid still under clinical investigation. Most promising of the nutritional products under clinical investigation is an intravenous fat preparation.

WARNER-LAMBERT PHARMACEUTICAL COMPANY

During 1956 Warner-Chilcott, which is the division of the Warner-Lambert company concerned with the marketing of so-called ethical pharmaceutical products, introduced Sterisil which is for vaginal infections; Plestran, a combination of thyroid-androgen-estrogen designed for improving the general state of the aged; and Releasin, a new hormone developed for overcoming miscarriage and abortion. The new ataraxic of this company is Pacatal. This company also has built and now occupies a new building devoted to standardization and research. Antiseptic and fungicidal agents are being studied. A new compound thus far known only as "L-6" acts as an antibiotic and is said to be particularly useful in oral and periodontal disorders.

The Phrenotropic Agents

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Progress in the treatment of the mentally ill with drugs has lagged behind the rapid advances made in such other fields of medicine as the infectious diseases and metabolic disorders. Within the last decade and especially within the last three years, however, unexpected gains have been achieved. These developments serve to point out that the problem is not insurmountable. It now appears that thinking disturbances, treated with drugs of very specific chemical configurations, may serve to elucidate some of the baffling functional brain changes in mental illness. As a nation we spend more than a billion dollars a year in the treatment and care of the mentally ill. Approximately 50 per cent of our hospital beds are occupied by such patients. Thus the need for better therapy to combat this devastating scourge is appallingly apparent.

In the minor mental disorders, such as the *psychoneuroses* and *neuroses*, sedative drugs have played an important role in psychiatric management. For example, the widespread use of phenobarbital for general nervousness, for the compulsive neurotic person, and for the hysterical patient is a well established application of drug therapy in these potentially modifiable emotional states. In *focal deficit reactions* such as epilepsy, striking improvements have been made in drug therapy and new drugs are being added in rapid succession to treat these convulsive disorders. In *disturbances of mood* such as hyperexcitability and depression, again definite therapeutic goals have been achieved by the use of drugs. The widespread use of the barbiturate depressants and dextroamphetamine as a stimulant to cerebral function bespeaks the possibilities of drug therapy in this field. Alcoholism, as a major mental illness, has also yielded partly at least to drug therapy, in its acute phase, and to some extent the underlying emotional defect may be influenced by drugs.

Only recently the major forms of mental illness, including *thinking disturbances* such as the paranoid and schizophrenic groups of patients, have shown definite improvement with drug medication. The ataractic drugs signaled this advance in therapy. Indeed, in most institutions these agents have revolutionized the treatment of schizophrenia. Intensive drug therapy has reduced the amount of custodial care, and the positive changes in behavior patterns make possible psychiatric therapy. The chances of an earlier hospital discharge are improved as a result of better therapy.

This recent upsurge of interest in drugs that influence thinking, mood, depression, excitability, and behavior has brought about a period of intensive research in this area. Dr. Harry Beckman in his *1957 Year Book of Drug Therapy* describes research in this field as assuming "an urgent and most unbecomingly hectic character." This scientific break-through did not occur in one place, in one field, or in one country. There seems to have been a series of interlocking developments—discoveries in France,

Switzerland, England, and the United States that paved the way for the new field of psychopharmacology.

Since the striking observations of Hoffman in 1943 of the hallucinogenic effects of d-lysergic acid diethylamide (LSD), many investigators have confirmed his findings. Volunteers who have taken this substance experience a mental intoxication that has features in common with the thinking disturbances of schizophrenia and paranoia. In the experimental psychoses produced by LSD, persons can describe their symptoms, yet retain a knowledge that the experience is induced by the drug. It appears that contact with reality is not lost. The amazing feature of the action of LSD is its potency. By mouth as little as 1 μg./Kg. will elicit the hallucinogenic effect.

We can describe then the pharmacologic effects of LSD as being those of hallucinations. The compound calls forth a bizarre mental confusional state. Such an agent has been termed a psychomimetic: a drug causing an action that mimics psychotic behavior. Another such substance is mescaline, trimethoxy-phenylethylamine, an alkaloid obtained from a species of cactus that grows in the Rio Grande Valley. Mescaline produces psychic changes similar to those of LSD and has been used as an experimental tool for investigations of schizophrenia-like behavior. Thus this alkaloid too might be classified as a psychomimetic agent. Other substances are known to produce psychopathologic states, or as Dr. Arthur Mirsky of the School of Medicine, University of Pittsburgh, puts it, "to influence the fantastica." These include such drugs as cocaine, tetrahydrocannabinol (a derivative of *Cannabis*), scopolamine, harmine (an alkaloid used by some South American Indians in their religious rites), and bufotenine (a substance obtained from the skin secretions of a species of toad). LSD is much more potent than any of these agents. Because it contains an indole nucleus in the molecule, in common with a number of other phrenotropic agents, it is of special interest.

Now it is unlikely that LSD is a prime factor in mental illness; nevertheless, this does not rule out the action of a metabolite of similar structure as a psychogenic agent. Although the psychotic state produced by LSD and schizophrenia are not identical, there appear to be sufficient common features to suggest that a biochemical factor is involved in the disease.

There is a substance known as serotonin, 5-hydroxytryptamine, which is found in high concentration in numerous tissues, especially the brain. This material is apparently formed from tryptophan by the chromaffin cells in the intestinal walls. The blood platelets seem to protect and distribute serotonin in the vascular system. It is suspected that the presence of serotonin in the brain is of prime importance in the maintenance of normal brain function. The true physiologic role of serotonin has yet to be established. The circumstantial evidence is very strong, however, that this substance acts as a neurohormone. For example, serotonin will antagonize the LSD-induced mental syndrome. Serotonin is broken down in the body by the action of the enzyme, amine oxidase, to 5-hydroxyindoleacetic acid and excreted as such in the urine. Brodie and his associates (1956), at the National Institutes of Health, have shown an increase in 5-hydroxyindoleacetic acid excretion after reserpine administration to dogs. Reserpine also liberates serotonin from the intestine, blood platelets, and brain tissue of rabbits. For these and other reasons, it has been pro-

posed that reserpine's action is mediated by releasing serotonin from its binding sites in the brain. Others have proposed that some types of mental illness may be expressions of a serotonin deficiency in the brain. The striking chemical similarity between serotonin and LSD certainly is provocative, but it is too early to predict the place of these agents in brain metabolism or brain function.

Of considerable interest is the observation of Stig Akerfeldt (1957), of Nobel Medicine Institute of Stockholm, Sweden. He has demonstrated a possible diagnostic test, a color reaction, to differentiate between the blood serum obtained from patients with mental disease and the blood serum from healthy, normal control subjects. Other workers have confirmed this. The test is not entirely specific but it is based on biochemical differences in the blood, and herein lies its possible significance to us at this time—that mental illness is related to a disturbed metabolic pattern.

It becomes increasingly clear, then, that mental disturbances are associated with some biochemical lesion. Chemical compounds containing the indole nucleus, of which LSD is an example, are capable of inducing schizophrenia-like states. Further, other substances that contain in their molecules the same indole nucleus, such as reserpine, can block the syndrome. The antagonism may be associated with a neurohormonal action of serotonin. At least a road has been opened to further exploration of the basic causes of mental disturbances.

For centuries *Rauwolfia* root has been used by Indian physicians in mental illness. The accepted name for the drug in Bihar and the United Provinces of India is *pagalkadawa*, or insanity remedy. In 1953 Dr. R. H. Hakin of India described a recovery rate of 31 per cent in psychotics treated with electroshock therapy alone, 51 per cent with *Rauwolfia* alone, and 80 per cent with the combined therapy. Dr. Nathan S. Kline (1956) became interested in the psychiatric use of the drug and began to study its effect on patients in the Rockland State Hospital in Orangeburg, New York. Using the drug on more than 400 mentally disturbed patients, he observed a significant tranquilizing effect of *Rauwolfia* and its alkaloid, reserpine. The number of violent accidents was reduced; restraints and seclusions were lessened also. He observed that the therapy reduced anxiety and obsessive compulsive drives. Further, it reduced excessive inhibition and reticence. Through these and subsequent observations *Rauwolfia* and its alkaloid, reserpine, were shown to be valuable in the treatment of the mentally ill.

There are scores of reports in the literature concerning the use of reserpine in the management of psychiatric patients in the hospital and in office practice. The consensus is that this agent is valuable in many cases of thinking disturbances; the side effects are not numerous or severe. It appears that the use of reserpine in mental illness has marked an epoch in psychiatric therapy. Various dosage schedules have been used, depending on the character of the patient's illness at the time therapy is instituted. The optimal dosage level is proportional to the intensity of the emotional disturbance. There is no incompatibility between the reserpine regimen and electroshock therapy. Each appears to complement the other. Psychotherapy is desirable concomitantly, and with reserpine the treatment is facilitated.

Reserpine therapy may cover a period of three to four months at the optimal dosage level. Barsa and Kline (1956) observed three periods of treatment response common

to many patients. These are the sedative, turbulent, and integrative phases. In the turbulent period the patient often feels worse under therapy than previously. As he emerges to the integrative period, definite improvement becomes manifest.

The use of chlorpromazine in mental illness appears to stem from its use as one of the components of the "lytic cocktail" for the purpose of producing artificial hibernation in certain surgical procedures. The effect of chlorpromazine in tranquilizing states of agitation and anxiety attracted the psychiatrist to its use.

Chlorpromazine is indicated mainly for psychomotor states of agitation. Broussolle,[9] one of the pioneers in the use of chlorpromazine in mental illness, states, "The patient admitted in a state of frenzy, vociferating, and gesticulating, finds himself in a few hours in a state of complete calm and rest," after the initial dose of chlorpromazine. There are no alarming symptoms of coma or complete paralysis. The patient is conscious and enjoys lassitude, which is not unpleasant. In this state the psychiatrist can make adequate communication with the patient.

Chlorpromazine has been found only moderately valuable in the treatment of depressive states. It does not appear to be able to combat serious cases of anxiety of melancholia.

Chlorpromazine produces remarkable effects in schizophrenic patients exhibiting catatonia and paranoia. In these persons, chlorpromazine produces a serenity without the clouding of consciousness. Moyer[12] found chlorpromazine to produce dramatic reversals of the symptoms and signs in the clinical variants of schizophrenia. About 40 per cent of the patients were definitely improved to the extent of having the symptoms of mental disease obliterated while under drug therapy.

In senile and arteriosclerotic states chlorpromazine has been found useful in tranquilizing agitation, combativeness, confusion, and aimless wandering. The patient becomes more cooperative and the problem of management is materially reduced.

Considerable importance is attached to early treatment in drug therapy of psychotic states. It seems that the chances of marked improvement from drug treatment decrease as the period of duration of the disease is prolonged. The most satisfactory clinical improvement has been achieved in those individuals who have been treated within the first year after the onset of the illness.

These were the first drugs useful in therapy and their discovery introduced the new science of psychopharmacology. In rapid succession other drugs were discovered. At least 12 new ataraxics have been marketed in the past three years (table I).

The bewildering confusion of new names appearing as the number of ataraxics increases is disturbing, and the industry is still spawning new products at a great rate. Unfortunately we have the added burden of two and sometimes three names for one drug. This can only lead to a compounding of confusion and represents a serious deficiency in modern drug therapy. It represents a deficiency in exact communication in an area where there should be no possible chance of misunderstanding.

Illustrating the results of recent laboratory and clinical investigations of new chemical compounds possessing marked effects on brain activity, we find such drugs as azacyclonol and pipradrol. These compounds have been selected as characteristic of a group of drugs labeled by Gerrard as the phrenotropic agents, meaning that they have an action on the mind. These two drugs, azacyclonol and pipradrol, are

chemically isomeric. That is, they possess the same total chemical configurations but the arrangements of the atoms within the molecule are different. Azacyclonol is termed the *gamma* isomer of pipradrol. Closely related chemically, their pharmacologic effects and uses differ widely. This is another striking illustration of how subtle is the biochemistry of the brain. The chemical relationships among the phrenotropic agents are illustrated in figure 1.

Both drugs influence that portion of the brain concerned with the function of alerting. A person may be said to be alert, moderately wide awake, drowsy, asleep, or psychotically out of contact with his surroundings, depending on the activity of a portion of the brain classified as the alerting system; the reticulodiencephalic-activating system. The effects of these two drugs on this alerting mechanism of the brain are different and in some respects directly the opposite.

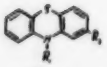
Pipradrol stimulates the alerting system, a stimulus which in turn is transmitted to the cerebral cortex; an animal or man treated with the drug exhibits symptoms of coordinated hyperactivity, is mentally more alert. The isomer, azacyclonol, on the other hand, is neither a stimulant nor a depressant to a normally functioning activating system. But in the presence of disease and an abnormally functioning activating system, azacyclonol may correct the abnormality. This drug is capable of antagonizing the hallucinogenic action of lysergic acid diethylamide. According

TABLE 1

Phrenotropic Agents

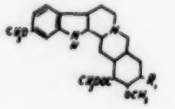
Generic name	Trade name	Company
Ataraxics		
Chlorpromazine	Thorazine	Smith, Kline & French
Promazine	Sparine	Wyeth
Mepazine	Pacatal	Warner-Chilcott
Proclorperazine	Compazine	Smith, Kline & French
Perphenazine	Trilafon	Schering
MC 4703	Vesprin	Squibb
Reserpine	Serpasil	Ciba
	Sandril	Lilly
	Reserpoid	Upjohn
Rescinnamine	Moderil	Pfizer
Raunormine (deserpidine)	Harmonyl	Abbott
Meprobamate	Miltown	Wallace
	Equanil	Wyeth
Phenaglycodol	Ultran	Lilly
Hydroxyzine	Atarax	Roerig
Benactyzine	Suavital	Glaxo (Europe)
Azacyclonol	Frenquel	Merrell
Stimulating agents		
Pipradrol	Meratran	Merrell
Methyl-phenidylacetate (methylphenidate)	Ritalin	Ciba

I. PHENOTHIAZINES



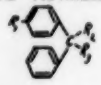
COMPOUND	R_1	R_2
CHLORPROMAZINE	$-CH_2-CH_2-CH_2N(CH_3)_2$	$-Cl$
PROMAZINE	$-CH_2-CH_2-CH_2N(CH_3)_2$	$-H$
MEPAZINE	$-CH_2-$	$-H$
PROCLORPERAZINE	$-CH_2-CH_2-CH_2-$	$-Cl$
PERPHENAZINE	$-CH_2-CH_2-CH_2-$	$-Cl$
MC 4703	$-CH_2-CH_2-CH_2N(CH_3)_2$	$-CF_3$

II. RAUWOLFIA ALKALOIDS



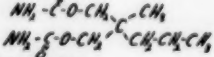
COMPOUND	R_1
RESERPINE	$-OOC-$
RESCINNAMINE	$-OOC-CH=CH-$

III. DIPHENYL METHANE DERIVATIVES



COMPOUND	R_1	R_2	R_3
HYDROXYZINE	$-Cl$	$-H$	$-N$
BENACTYZINE	$-H$	$-OH$	$-C(=O)-O-CH_2-CH_2-N(C_2H_5)_2$
AZACYCLONOL	$-H$	$-OH$	
PIPRADROL	$-H$	$-OH$	

IV. MEPROBAMATE



V. PHENAGLYCODOL

VI. METHYL PHENIDYLACETATE

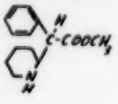


Fig. 1. Chemistry of the phrenotropic agents.

to Rinaldi et al,[6] azacyclonol is an anticonfusion drug that restores to normal the activity of the mesodiencephalic activating system and thus relieves the cortex of excessive stimulation. As an antihallucinatory or antidelusional drug, azacyclonol is quite different from pipradrol in its effects on an individual.

Translating these pharmacologic effects to clinical applications we find that the drug pipradrol is of value in the symptomatic treatment of emotional fatigue and mild depressive states. In such persons there is no characteristic physical disease; they are unhappy, discouraged, and complain of chronic fatigue. In patients of this type, generally the elderly, the smallest task, physical or mental, is simply too much. It has been found that relatively small doses (2 mg.) of pipradrol per day by mouth will produce a very mild degree of stimulation in these individuals. Although they are unaware of the effects in themselves, objective measurements of their performance indicate a marked improvement in mental outlook and an elevation of mood. The pessimistic view and withdrawn feeling of helplessness is mitigated to a degree. While not all patients are so favorably influenced by pipradrol, the drug is a useful agent in geriatric medicine. Of significance is the absence of a euphoric effect or a period of afterdepression, two effects associated with the use of amphetamine as a stimulant.

Other medical indications of pipradrol are in the depressed chronically ill, to combat drug-induced sedation, and in some behavior disorders in children. Fabing[4] has found large doses of pipradrol to produce occasional dramatic improvement in psychotic depressions, but in general, electroshock therapy is preferable.

The medical applications of azacyclonol as an antihallucinatory agent are quite significant. The three outstanding indications have been given by Allin and Pogge.[1] These are in schizophrenia, toxic psychoses such as alcoholic hallucinosis, and postoperative confusion and delirium.

Azacyclonol administered orally in doses of 20 mg. three times a day for prolonged periods is capable of terminating the hallucinations and delusions of the schizophrenic patient. A significant number of patients who receive treatment within a four to five year period after the onset of the disease can be helped by drug therapy. The results are not as encouraging if the mental illness has been of longer duration. Antihallucinatory drugs of the type of azacyclonol interrupt the patient's contact with his delusional world and he becomes available for psychotherapy.

Alcoholic hallucinosis, a toxic psychosis, responds dramatically to intravenous administration of azacyclonol. The hallucinatory pattern in these individuals is one in which they experience visual and auditory sensations of a bizarre character. They see things and hear noises that do not exist. In some cases a single dose of 100 mg. of the drug may be sufficient to cause a relief of the symptoms.

Delusions and hallucinations appearing several days after a major surgical operation are designated postoperative confusion and delirium. This condition is fairly commonly encountered in elderly patients and it can be readily controlled by azacyclonol.

Much remains to be learned regarding the mechanism of action of these drugs. Sharp differences exist among this class of agents. For example, azacyclonol is not used in psychotic depressive states or anxiety reactions devoid of hallucinatory or

delusional phenomena. On the other hand, meprobamate has been widely employed for its antitension effects and to suppress the anxiety syndrome associated with the withdrawal of alcohol from the chronic alcoholic.

The ataractic drugs differ fundamentally from the barbiturates and similar depressants in that their primary action is not on the cerebral cortex but on the lower levels of the brain. The principal effect of the ataraxics is to make the impact of emotional stress less disturbing while at the same time the individual remains alert. Patients under such medication are able to exercise and care for their personal needs, and the severe depression of barbiturate overdosage is eliminated.

Only certain uses of some ataractic drugs in mental illness have been described. These reports in the literature are numerous. On the other hand, there is a marked lack of published factual information on the use and effects of tranquilizing drugs in nonhospitalized patients, people suffering from tension, anxiety, lack of emotional composure, persons unable to cope with their burden of unsolved problems. It is this very large group who have taken the millions of tablets of ataractic drugs in the past two to three years. It is for these individuals that the ataraxics are prescribed now in 1 of every 15 prescriptions written. Apparently many people are attempting to cope with the stress-laden situations of modern living by resorting to the use of ataractic drugs. It has been said that this is so because of the paucity of trained psychiatrists and the cost and length of psychiatric treatment.[22] There are those who are uneasy about this situation. Aldous Huxley warns that man in possession of such drugs can tranquilize himself into inertia. But the whole history of mankind is intimately entwined with the use of such drugs as alcohol, marihuana, and opium. There is little evidence that man has wittingly drugged himself into mass stupor by the use of these agents. It seems that the disturbing impact of the tranquilizers on our people today is related to the terrifying speed with which these drugs have been introduced and accepted. Perhaps rightly we should call for a more temperate application.

These drugs have been prescribed in such an astonishing variety of conditions that it is difficult to see how they could be useful in all cases. For example, to list only a few, the ataraxics have been employed to "banish that tired feeling," to cure headache, to ease the ordeal of giving a speech, to lessen the aggravated fears of the poliomyelitis and cancer victim, to assuage the terrors of having a tooth pulled, to overcome frigidity, and to improve muscle function of children with cerebral palsy. They have even been used to quiet barking dogs and to calm high strung race horses. Their use has been suggested to make workers happier and hence more productive and to cure juvenile delinquency.

If all this is so, one might ask what has become of the concept of the rugged individualist? Are we as a people so timid, so fearful, so neurotic that we are unable to face the smallest challenge, the slightest degree of physical or psychic trauma? Must we find soothing tranquilization in a tablet for all life's problems and decisions? The qualities of character are won by facing and overcoming the ordeals and challenging problems of life, not in seeking escape by any devious means at hand.

These problems are receiving attention. There has been no dearth of symposia, meetings, and conferences on this subject. The recently established Psychopharma-

cology Service Center of the National Institutes of Health has arranged high level conferences of selected investigators representing the pharmaceutical industry, psychiatrists, pharmacologists, clinicians, and research workers in the area of mental health, to meet and attempt to work out some guiding principle. Curiously one problem seems to be that the discovery of potentially useful drugs has outrun the means of evaluation. The presently unsatisfactory tools of the behavioral sciences need to be sharpened to evaluate critically these new weapons in the fight against mental illness. But the greatest dilemma is man himself. The potential cure of mental disease is a clear-cut medical application of the ataractic drugs. The perplexing predicament of the fringe areas seems to offer the greatest capacity for misuse. It is in these applications of the ataraxics that psychiatric judgment and guidance are needed most. These are immediate and pressing problems and the answers are not at hand.

The problem of the potential toxicity of these drugs is a peculiar one. There is a certain calculated hazard associated with the use of any drug. In the case of a patient with a severe mental disease the risk that can be legitimately assumed is greater than would be permissible in a person asking for relief from simple nervous tension. Thus some of the side effects of reserpine, such as smooth muscle stimulation and hypotension, and the symptoms of parkinsonism, skin rash, and jaundice that may be caused by chlorpromazine administration constitute definite toxicity hazards. This is especially true with the high doses administered in psychiatric disorders. On the other hand, we now have had a number of reports of untoward reactions following, in some cases, moderate doses of some of the ataractic drugs. As might be expected a few idiosyncratic individuals have been found who have reacted violently to even small doses of some of these drugs. In view of the large number of people who have been treated with these agents, it is rather surprising that so far the reported untoward reactions have been so few. The American Psychiatric Association has warned that these drugs should be prescribed only when the medical needs are clearly established. But the pressure generated in the public's mind by the press, radio, and television entertainment media reflects itself in the lay demand for the ataraxics. It is quite understandable why the busy practitioner has yielded to this demand. Nevertheless, a certain element of caution is indicated lest we embrace the use of these drugs too enthusiastically.

We can conclude that the successful use of these drugs in the treatment of mental illness appears to be a major medical milestone. Without question, the ataractic drugs have brightened the outlook for psychotic patients; they have contributed to the availability of psychotherapy and eliminated much of the danger and disgust that was the lot of those who cared for the mentally ill. The problem of mental disease is far from solved but an opening wedge has been developed. Further, it appears that we will have a large number of patients discharged from mental hospitals and controlled by maintenance doses of the ataractic drugs. It is possible that these persons may live out their life span integrated into the community and not supported at public expense in institutions. Perhaps it is not too much to hope that the treatment of patients with psychoses will be brought to the level of other types of therapy —rheumatoid arthritis, heart disease, or even the acute infectious diseases.

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Law School Periodical Features Medicolegal Articles

Medicolegal articles by physicians for lawyers, and by lawyers for physicians, are featured in the *Cleveland-Marshall Law Review* of Cleveland-Marshall Law School, Cleveland, Ohio. Less than a year old, the *Review* is under the charge of Professor Howard L. Oleck, well-known writer on medicolegal subjects, aided by a Medical Advisory Board of nationally famous physicians, physician-law students, and leading legal authorities.

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The *Review* is now in circulation to medical libraries and to physicians, a very unusual procedure for a law school journal. Among its staff advisors are Dr. Walter C. Alvarez, Dr. Henry K. Beecher, Dr. Ralph M. Kniseley, Dr. L. J. McCormack, Dr. Robert E. Wise, Dr. Guy A. Caldwell, Dr. W. Kenneth Clark, Dr. Samuel R. Gerber, Dr. W. Randolph Lovelace, Dr. Paul Nelson, Dr. Harry F. Zinsser.

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SODIUM BICARBONATE FOR MOTION SICKNESS. Injection of sodium bicarbonate may prevent motion sickness for as long as one month, reports Dr. Minoru Muta, Osaka, Japan (Modern Medicine, June 15, 1957). By decreasing the concentration of potassium in the fluid in the inner ear, the new therapy reduces sensations after rotation. The injection was completely effective in 69 of 100 susceptible persons, partly beneficial in 23.

GAMMA GLOBULIN USEFUL IN SKIN DISEASE. Gamma globulin injections may be useful in shortening the course of pityriasis rosea if given early enough, reported R. W. Salin, A. C. Curtis, and A. Wheeler, University of Michigan, at the A.M.A. annual meeting. The disease lasted an average of 17.3 days in patients given gamma globulin in the first week of eruption; average untreated case lasts 31 days.

BRAIN INJECTION HELPS CEREBRAL PALSY VICTIMS. Chemopallidectomy, which involves injection of alcohol deep into the brain and has been used for adult victims of Parkinson's disease, may help cerebral palsy victims to relieve involuntary muscular movements. Twenty of 30 children who received the surgery were either cured of the involuntary movements or were noticeably helped (J. A. M. A., July 20, 1957). Method destroys tissue, combats chorea, rigidity, athetosis.

INFECTIOUS MONONUCLEOSIS AFFECTS NERVOUS SYSTEM. Of 32 cases of infectious mononucleosis in children 16 or younger, 6 had definite neurologic complications, 6 had suggestive signs or history (Northwest Med. 56:695, June, 1957). One patient died, 1 was left with irreversible brain damage. Syncope, headache, other symptoms common in the disease may represent neurologic involvement. In cases of unexplained neurologic disease in children, infectious mononucleosis should be considered.

RADIOACTIVE WASTES CREATE PROBLEM. Atomic wastes indiscriminately dumped at sea or buried in the earth could spread around the world "with no regard for international boundaries," said Lewis L. Strauss, chairman of the Atomic Energy Commission, at recent Congressional hearings. The U. S. now has safeguard agreements with more than 40 countries, but an international agency is deemed essential.

ANALGESIC EFFECT OF VITAMIN K. Vitamin K is reported to have "considerable pain relieving properties," greater than those of morphine (Wisconsin M. J., June, 1957). Studies in 73 per cent of 115 patients with inoperable carcinomas and sarcomas with great pain demonstrated sufficient analgesic effect with vitamin K to permit discontinuing morphine and barbiturates.

MECHANISM OF VIRUS DESTRUCTION. The mechanism by which viruses destroy cells and spread infection has apparently been discovered in research at the University of California. The scientists report in the Journal of General Physiology on studies with a new chemical, an enzyme called virolysin, that they found in virus-infected cells. Virolysin is present only in infected cells, destroys cells by chemical action. Study also showed that viruses can force a cell to manufacture virolysin.

HORMONES HALT GROWTH OF TALL GIRLS. Use of hormones significantly decelerated linear skeletal growth in 5 adolescent girls, according to a report to the American Pediatric Society. Stilbestrol was given in dosage of 5 to 10 mg. daily for 8 to 29 months, and at the same time progesterone was given five days each month. One girl stopped growing two inches below the predicted six foot height, another three inches before predicted height.

P. O. HITS QUACKERY BY MAIL. Use of the mails by medical quacks has reached an all-time high, according to U. S. postal officials who describe fake medical cures as the biggest fraud conducted by mail at present time. Best sellers include obesity remedies and "cures" for arthritis, skin trouble, baldness, cancer, and sexual impotence. Annual business is estimated at $50 million. During past year P. O. Department issued more than 40 fraud orders that bar promoter from receiving any mail.

"PSEUDOPREGNANCY" FOR PELVIC ENDOMETRIOSIS. In treatment of pelvic endometriosis patients in whom pregnancy was not possible, "pseudopregnancy" was induced with large doses of estrogen combined with newer progestins for periods up to four months, it was reported at the meeting of the A. M. A. Ovulation was inhibited, amenorrhea induced, typical pregnancy symptoms occurred. Endometrium showed decidual changes with focal necrosis, glandular hyperplasia. Improvement was noted in all patients, in some cases up to 7 months after end of treatment.

Dextro-Amphetamine Sulfate in Mild Depression and Anxiety

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Aberrant human emotions are difficult of sharp clinical assay. The numerous definitive classifications of mental disease attest to the difficulty of general agreement on well-defined diagnostic entities.

However, the infinite variety of emotional disturbances does lend itself to rough grading. Between the two extremes of deep depression and complete withdrawal on the one hand and violent psychotic agitation on the other, there are innumerable shadings, gradations, and combinations.

In the interest of simplified clinical understanding, one can predicate a broad spectrum of the psyche between these extremes. Starting from the "negative" end of the spectrum (deep withdrawal) there are less severe degrees of depression and hypoactive anxiety; these shade gradually into the wide central spectrum of so-called "average" or "normalcy." Here socially acceptable patterns of behavior exist. Further along the emotional spectrum, toward the "positive" side, are moderate states of anxiety, tension, and hyperactivity, followed by more intense degrees of agitation, and finally ending in the extreme area of psychotic hypermotricity and overt manic conduct.

Since the advent of chlorpromazine and reserpine three years ago, considerable progress has been made in the chemotherapy of mental disease. Many observers regard this as the opening of a new era in psychotherapy. Through the agency of these drugs, attention was primarily focused on patients with psychomotor hyperactivity ("positive" side of the spectrum). In practical experience, these compounds were generally most effective as ataraxics for overt, extreme forms of agitation.

Shortly thereafter, a series of additional compounds with ataractic properties made their appearance (meprobamate, promazine, perphenazine, phenaglycodol, hydroxyzine). Clinically these preparations were best applicable to the ambulatory psychoneurotic or neurotic patient next in line on the "positive" side of the spectrum. Patients with a moderate agitation or anxiety-tension syndrome responded most favorably.

This concentrated interest given to the therapy of the various states of agitation and stress has resulted in relative neglect of the depressed and withdrawn patient ("negative" side of the spectrum). Although various modalities of shock still play very important roles in treating the most extreme forms of negativistic behavior, the milder forms have responded poorly to the mild ataraxics and have thereby attracted less attention. One might speculate that clinicians are less concerned about these emotional difficulties because they are not quite as urgent in upsetting the social pattern or because they are less obvious trouble to the family or physician.

The present study was undertaken to evaluate more exactly the mood-elevating

TABLE I

Frequency of Symptoms in 25 Patients

Symptom	No. patients
Mood of depression (gloomy, afraid, worried)	23
Socially backward (shy, withdrawn, overmodest, retiring, insecure)	22
Fatigue	21
Vague somatic aches and pains	20
Constant headache (diffuse or somewhat localized)	18
Irritability (crankiness)	16
Hunger (constant craving for sweets)	16
Indigestion (abdominal pains, belching, obstipation, diarrhea, heartburn)	12
Insomnia	10
Palpitation	9
Somnolence	8

effect of dextro-amphetamine sulfate, the oldest and best known of the "euphoriant" or analeptic drugs. Twenty-five patients were closely observed for periods of two to six months.

Particular attention was paid first to the selection of patients; second, to the ability of dextro-amphetamine sulfate to elevate mood and relieve depressed anxiety, fatigue, nervousness, and vague aches and pains, just as the ataraxics reduce agitation and tension on the contralateral "positive" side of the psychic spectrum.

SELECTION OF PATIENTS

Fifteen of the patients were carefully selected from a large representative general practice; the other 10 were cases of senile depression under custodial care in a large, well-run geriatric facility.

All 25 patients had in common basic emotional negativism with a well-established climate of anxiety, depression, or both. They had multiple subjective complaints, all of which were clearly on the negative side of center in the emotional spectrum. Table I lists these symptoms in order of frequency.

Examination of this mélange of symptoms reveals that more than half of the 25 had at least seven complaints in common; in contrast, 10 patients complained of insomnia and 8 of somnolence.

Clinically, the medical diagnoses of the group (see table II) fell mainly into three large groups: menopause, exogenous obesity, and senile depression. It is interesting to note that "negative" emotional states were associated most often with the menopause and obesity. Symptomatically, patients in these two groups complained most often of depression, insecurity, fatigue, insatiable hunger, vague unrelated aches and pains. Obesity was rarely found in the senile patients, whose ages ranged from 60 to 81 years. The geriatric group included generally the poor eaters, with marked fixation on bowel habits, gastrointestinal complaints, hypochondriasis, self-pity, fatigue, and insomnia. For these patients, being at home with spouses or married

TABLE II
Medical Diagnosis

Diagnosis	No. patients
Menopause	8
Obesity (exogenous)	8
Senile depression	6
Anxiety state	2
"Compensation" psychoneurosis	1

children was intolerable; residence in a nursing home was the only practical solution.

The younger group of 15 patients, aged 16 to 49 years, had the common characteristic of poor social adjustment. In general, they preferred being or working alone. Socially they got along poorly with friends, family, and business associates. Many of them revealed an emotional state of love deprivation. By constantly eating or nibbling on sweets they indulged in an oral form of self-love in the absence of a mature and adjusted sex life or parent love pattern. Obesity became the obvious problem that prompted them to seek medical help.

METHOD OF STUDY

In order to simplify the administration of dextro-amphetamine sulfate,* a basic dosage of 15 mg. daily was given to each patient in the sustained release form before breakfast. This obviated the need for repeated medication during the rest of the day and assured slow, continuous absorption of the drug for a 10 to 14 hour period without interference with sleep. A small dose of barbiturate (amobarbital, 1½ gr.) reduced any tendency toward insomnia, nervousness, and overstimulation. There was little or no tendency to forget the medication on the one-a-day schedule.

The patients were examined and interviewed at weekly intervals. Special attention was paid to (1) alterations in personality pattern, (2) improvement in psychosomatic complaints, and (3) possible side effects.

Urinalyses, blood chemistries (including renal and hepatic function tests), and hemograms were performed before and during the course of the study. The drug was given continuously for periods of two to six months.

RESULTS

The emotional climate in the 23 cases complaining of depression and in the 22 of social withdrawal showed a marked reversal in 18 (80 per cent). The patients reported variable but noteworthy degrees of emotional "lift"—a psychologic re-energizing—beginning during the first week of treatment. In their own words, they felt more optimistic, more confident, and less afraid. Their outlook became brighter, their attitude more alert; they felt greater energies for the day's work. They were more relaxed with other people and felt a need to talk. The level of response was not perfect or complete, but improved week by week as confidence was restored. The

* The trade name of Smith, Kline & French Laboratories for dextro-amphetamine sulfate and amobarbital is Dexamyl Spansule.

weekly interviews gave these patients an opportunity to talk and many began to enjoy the sessions, which provided opportunity for expression and analysis.

Four of this group showed little or no response in this direction and were listed as failures (about 20 per cent).

The symptom of psychosomatic headache (organic cause had been eliminated carefully) dissolved in 13 of 18 patients.

Of 21 patients complaining of fatigue, lassitude, and sluggishness, 16 (76 per cent) felt more energized and "pepped up." They were better able to do their day's tasks and began each day with diminished fear and insecurity. The psychomotor stimulation they received seemed to dissolve the phlegmatic habitus.

Vague aches and pains, for which no organic pathology could be found, yielded to dextro-amphetamine sulfate in 60 per cent of the 20 patients who had constantly complained. There also seemed to be less concern and conversation about the mild pains that persisted.

Irritability and crankiness were not as noticeably improved. Only 6 of the 16 who admitted to these felt they were helped.

The craving for sweets was the most effectively controlled of all symptom complexes. Fifteen of 16 patients (94 per cent) reported excellent appetite control. Eight of these 16, whose initial obesity was the chief complaint, lost 3 to 4 pounds weekly while on dextro-amphetamine sulfate. The resulting improvement in appearance and figure bolstered morale and raised the level of interpersonal relations.

Insomnia was helped in 60 per cent; palpitation in 45 per cent (it was augmented in 2 patients); and somnolence was eradicated in 87 per cent.

It is noteworthy that none of the 10 senile patients were overweight. Generally this older group of patients complained more of fatigue, multitudes of aches and pains, vague gastrointestinal tensions, and somnolence. Their responses were not quite as gratifying as with the younger group, with the exception of somnolence, which was readily corrected.

SIDE EFFECTS

Side effects resulting from prolonged, continuous administration of dextro-amphetamine sulfate were minimal. Two patients reported increased palpitation; 1 of these responded to the addition of a mild ataraxic (hydroxyzine); the other discontinued use of the drug. Four of the 10 patients with insomnia reported accentuation of sleeplessness and had to take larger doses of hypnotics to overcome this. No incidents of allergic or dermatologic reactions were reported, nor were there any gastrointestinal disturbances.

Repeated urinalyses, blood chemistries, and hemograms revealed no alteration of pre-existing levels. Blood pressures were not appreciably elevated in any instance; in the obese group, there was a uniform drop of 10 to 20 mg. of mercury in the systolic and diastolic levels after a measurable weight loss. The overweight patients showed a mild elevation of blood pressure initially, and the hypotensive effect of weight loss was desirable.

CASE HISTORIES

Case 1. E. M., a 44 year old salesman, presented with the chief complaint of a constant craving for

sweets, with resulting obesity. He weighed 204 pounds and was 69 inches tall. Blood pressure was 160/96, pulse 88, with a regular sinus rhythm; otherwise he was physically normal. Subsidiary complaints included easy fatigability, no ambition, and a drop in income for the previous three years; socially he had no real friends, and he shied away from parties and groups; he liked to read or watch television alone. He was not married and lived with old parents. Personality profile revealed shyness since childhood; he had always clung to his parents, did poorly in school, rarely went out with the opposite sex; he was retiring, always worried about his future, but was defeatist in outlook. He had frequent headaches when faced with an economic or social problem and fell asleep whenever bored.

On a regime of 15 mg. daily of dextro-amphetamine sulfate in the sustained release form, plus a 1500 caloric diet, the patient shed excess weight at the rate of 12 pounds/month. The blood pressure dropped to 130/80. With the improvement in his appearance, he felt more sure of himself, and his fatigability and headaches were the first complaints to disappear. He reported with pride that people were complimenting him on his appearance and that his sales were improving. He began to accept invitations to go out and stated that he was enjoying the new social life. The desire to sleep during the day disappeared and he showed new zest and interest in life. At this point it was suggested that he undergo some psychotherapy to dissolve some of the involved and disturbed parent relationships. He agreed to this and is now doing well under the care of a competent psychiatrist.

Case 2. F. S., a 72 year old woman, had the chief complaint of severe depression, with fatigue, generalized abdominal pains, headache, and social withdrawal. This patient was of average build, ate sparingly, and had developed the habit of retiring to her room in the nursing home after each meal and lying in bed bemoaning her miserable fate, her aches and pains, and neglect by her family and physician. She was irritable and cranky at all times and was unpleasant to anyone who approached her.

Physically there was no serious impairment of any organ system. Blood pressure, cardiovascular system, musculoskeletal system, and viscera were essentially negative.

On 15 mg. sustained release capsules of dextro-amphetamine sulfate daily, she began to manifest her first change in attitude by sitting in the dayroom and watching television with other residents of the nursing home. Shortly afterward, she initiated conversations with other residents and began to eat with more appetite and enjoyment. The constant complaining about her abdominal pains receded gradually, as did her headaches and the frequent rest periods in bed.

Her general attitude changed from the complete negativism to a restrained acceptance of her environment with a minimal desire to join in group activities. She took more interest in her clothes; she began to read newspapers and discuss current events instead of her aches and pains. When complimented on the excellent change in her personality, she showed some resentment and gave an irritated reply.

CONCLUSIONS

1. A spectrum of human emotions is suggested for better clinical understanding and drug evaluation. The ataractic drugs are useful on the "positive" side of the spectrum where hyperactivity and agitation predominate the emotional climate. These drugs are ineffectual for the "negative" counterpart of hypoactivity, depression, and anxiety.

2. Dextro-amphetamine is ideally suited for the mild cases of depression characterized by multitudes of psychosomatic symptoms, fatigue, social withdrawal, obesity, and emotional sluggishness. It is a safe drug for continuous administration and is ideally suited for ambulatory and senile patients whose symptoms fall into the moderately "negative" band of the emotional spectrum. The drug facilitates further psychotherapy, where indicated, by relieving anxiety, withdrawal, and hypoactivity.

ACKNOWLEDGMENT

The dextro-amphetamine sulfate used in this study was provided by Smith, Kline & French Laboratories, Philadelphia.

Preliminary Observations on the Positive Inotropic Effects of Mephentermine

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Mephentermine,* N-methyl-phenyl-tertiary butyl amine sulfate, is an effective pressor amine that can be administered by the intravenous or intramuscular routes. The pharmacologic properties[1] of this drug are similar in certain respects to those of other sympathomimetic amines. However, specific actions of mephentermine on the cardiovascular system make it unique among the group of pressor amines currently in use.

The ability of mephentermine to protect against and correct arrhythmias induced by epinephrine and epinephrine with cyclopropane anesthesia has been emphasized by Glassman and Seifter[2] and by Lynch and co-workers.[3] Furthermore, it has also been demonstrated that mephentermine will not produce ventricular fibrillation during cyclopropane anesthesia.[3] Various cardiac arrhythmias produced in dogs, including auricular fibrillation, auricular flutter, and ventricular extrasystoles, have been eliminated by the use of mephentermine, as have ectopic beats produced by acetyl-strophanthidin intoxication.[4] Mechanical alternans likewise has been reverted to normal by mephentermine.[4] These antifibrillatory actions are the result of direct effects on the conduction system of the heart and on the myocardium.[5]

Increase in the force of myocardial contraction after administration of mephentermine was first reported by Goldberg and co-workers.[6] This positive inotropic effect has since been noted and emphasized by others.[2, 7, 8]

It is known that in the presence of ether anesthesia, myocardial depression can be predicted in certain condit ons such as hypothyroidism, Cushing's syndrome, and Addison's disease. The return of certain substances to the circulation, namely, epinephrine or norepinephrine, would result in an increase in the force of myocardial contraction. In our experience in chest operations, hypotensive episodes that occur in the absence of obvious cause, such as blood loss, visceral manipulation, and the like, are accompanied by a visibly decreased myocardial contraction. This type of shock seems to be the result of failure of the heart as a pump.

The cardio-salutary effects of mephentermine, particularly the positive inotropic effect, were of particular interest to this observer. It has been suggested that the increase in contractile force of the heart produced by pressor amines is the basis for recovery from shock.[9] We have found, as have others,[10–12] that mephentermine is most effective in the prevention or correction of hypotension occurring with spinal and general anesthesia in surgery and obstetrics. However, there have been no direct observations on the effect on contractility of the heart during the pressor

* The trade name of Wyeth Laboratories for mephentermine is Wyamine.

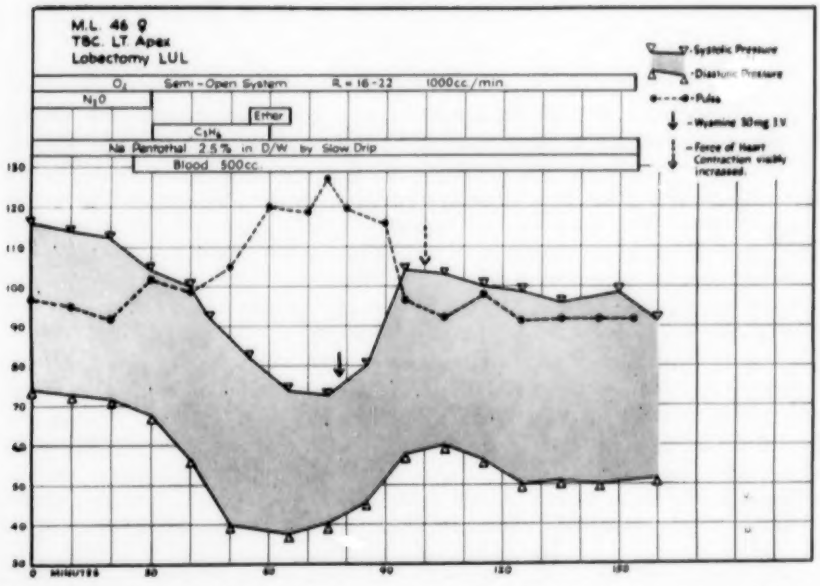

FIG. 1. Effect of administration of mephentermine to patient who received a single intravenous injection of 30 mg.

response with mephentermine. The open chest surgical procedure provided an excellent stage for direct observation of cardiac responses.

A series of 47 open chest procedures, including pneumonectomy, lobectomy, and segmental resections of the lung, were observed. In 7 patients undergoing such operations, decreased contraction of the heart developed. Although the heart beat forcefully when the chest was first opened, the contractions became progressively less vigorous and appeared weak and "flabby." This decrease in contractile force was accompanied by a drop in blood pressure and, in most cases, a rise in the cardiac rate. The depression of myocardial activity developed in the presence of adequate ventilation and oxygenation. Hypoxia or hypercapnea could not be considered as factors in the production of the observed decrease in myocardial activity.

Mephentermine was administered intravenously to each of the 7 patients when the force of myocardial contraction was visibly decreased. The blood pressure was falling and the pulse rate increased. One patient received a single intravenous injection of 30 mg. mephentermine (fig. 1) and 6 received an initial intravenous injection of 22.5 mg. Within 10 minutes there was a visible increase in the force of myocardial contraction accompanied by a rise in blood pressure and a decrease in the cardiac rate. However, 1 patient who had received 22.5 mg. at first required a continuous intravenous drip of mephentermine, 15 mg. in 500 cc. of 5 per cent dextrose in water, after the initial inotropic response (fig. 2), and it was necessary to give the other 5 patients a second intravenous injection of 22.5 mg. in order to pro-

duce the maximum positive inotropic effect with the desired pressor action (fig. 3).

DISCUSSION

The dramatic effects of mephentermine on myocardial contraction, with the attendant pressor response, made it a useful therapeutic agent in our hands. Mephentermine can be administered with ease by either the intravenous or intramuscular route. It can be injected directly and without dilution into the vein and there is no danger of intra- or extravascular reaction at the site of injection. The response is rapid once the adequate therapeutic dose has been given. In our first 2 cases, the desired pressor response together with the observed positive inotropic effect was obtained with a single dose of 22.5 mg. mephentermine. In subsequent cases, it was necessary to administer a second similar amount 10 to 20 minutes after the initial injection in order to obtain the optimum pressor and inotropic effects. Our further experience with mephentermine, as well as the experience of others,[12, 14] indicates that 45 mg. of mephentermine given in a single intravenous injection produces the desired pressor and positive inotropic response. Likewise, adequate prophylaxis of hypotensive episodes that may occur during certain surgical procedures may be obtained by the use of a single intramuscular injection of 45 mg. of mephentermine.

The use of this pressor amine is not contraindicated in the presence of cyclopropane

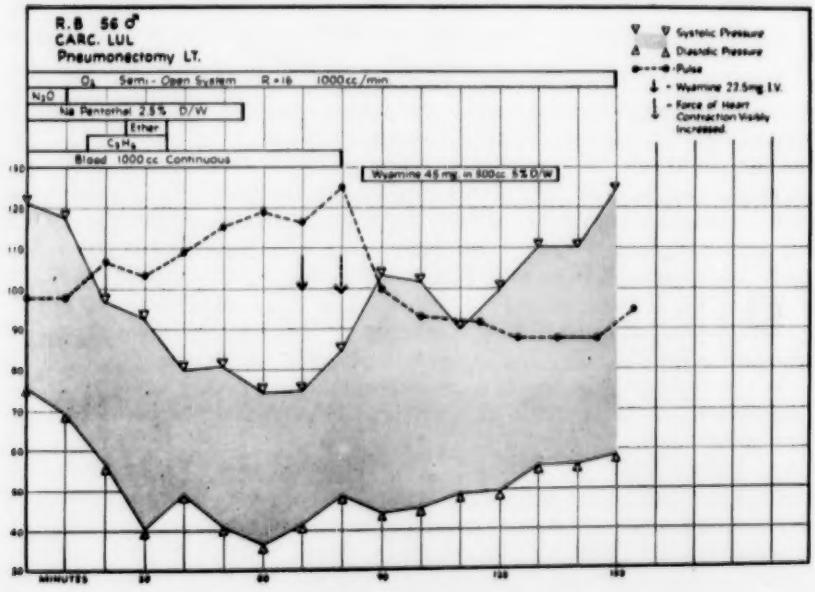

FIG. 2. Effect of administration of mephentermine to patient who, after receiving 22.5 mg. at first, required a continuous intravenous drip of mephentermine, 15 mg. in 500 cc. of 5 per cent dextrose in water, after the initial inotropic response.

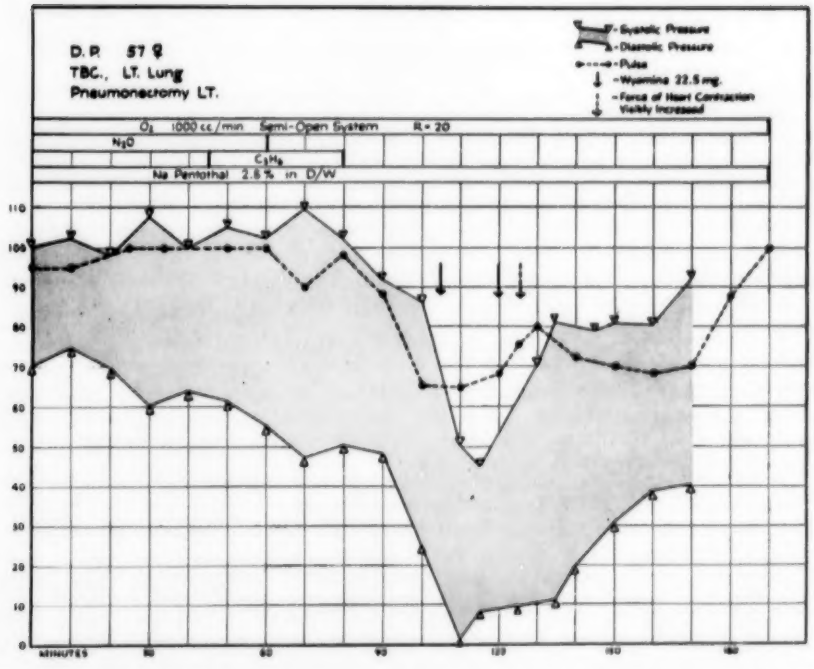

FIG. 3. Effect of administration of mephentermine to patient who required a second intravenous injection of 22.5 mg.

anesthesia. Indeed, others[3] have shown this agent to be an effective antifibrillatory agent in the presence of cyclopropane anesthesia.

The effects of mephentermine on cardiac irregularities have been reported.[3–5] It has been noted that at the peak of the pressor response produced by mephentermine, transient extrasystoles may be seen.[3] This phenomenon, lasting less than a minute, was observed in all 7 of our cases.

SUMMARY AND CONCLUSIONS

1. Observations of the positive inotropic effect of mephentermine indicate that this agent increases the force of myocardial contraction, and hence is a useful cardiotonic agent.

2. The pressor response to mephentermine is predictable and rapid.

3. The use of mephentermine as a pressor amine in the presence of cyclopropane anesthesia is safe, effective, and protective against cardiac arrhythmias.

4. The effective dose of mephentermine for optimum pressor response and positive inotropic effect is 45 mg. intravenously or intramuscularly.

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Academy of Psychosomatic Medicine

The program of the fourth annual meeting of the Academy of Psychosomatic Medicine, to be held Oct. 17 to 19 at the Morrison Hotel in Chicago, will be devoted to "Psychosomatic Aspects of Obstetrics, Gynecology, Endocrinology and Diseases of Metabolism." This is the first meeting ever to be held in this country where every one of these specialties will be presented by a multidisciplinary approach. The panels and symposia will include obstetricians, gynecologists, endocrinologists, periodontists, psychiatrists, psychologists, anesthesiologists, and other specialists in various fields of medicine. There will also be 24 round-table discussions covering all aspects of the specialties.

The meeting will be open to all scientific disciplines, as well as to psychologists, social workers, and nurses. Information may be obtained from Dr. William S. Kroger, Secretary, 104 South Michigan Avenue, Chicago 3, Illinois.

Prednisolone: A Preliminary Appraisal of Its Use Topically

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The new synthetic corticosteroids, prednisone and prednisolone,* have 3 to 5 times the antirheumatic and anti-inflammatory activity of cortisone and hydrocortisone without producing an increase of undesirable side effects.[1–4]

Preliminary studies by Robinson[2] and Goldman and co-workers[3] demonstrated that prednisone and prednisolone ointments were nonirritating, antipruritic, and anti-inflammatory. Frank and Stritzler[4] found topical prednisolone and hydrocortisone equally effective as anti-inflammatory agents but they thought the latter a superior antipruritic. Noojin[5] noted 85 per cent benefit in a group of itching dermatoses treated with local applications of prednisolone ointment or lotion and found that there was no loss of antipruritic effectiveness in combinations with antibiotics. Robinson and Robinson[6] concluded that prednisone was ineffective topically but that prednisolone was an excellent antipruritic and anti-inflammatory medicament when used alone or in combination with antibiotics. Employing an early experimental preparation, they noted signs of irritation in one third of their subjects. Subsequent observations with a refined prednisolone showed it to be highly effective against itching with little or no evidence of irritation. Those studies were conducted with experimental crystalline prednisolone incorporated into various bases.[3–6]

Topical prednisolone is now stated to be less irritating than the prednisolone used in previous observations.

The purpose of this study was to appraise clinically the antipruritic effectiveness of topical prednisolone incorporated into bases supplied by the manufacturer as a preliminary to a more comprehensive and controlled study. This report is based on the results observed in private practice with 127 cases of selected dermatoses in which the principal complaint was itching, burning, or pain.

MATERIALS AND METHOD

Prednisolone, an analogue of hydrocortisone, was supplied as 0.5 per cent (free alcohol) ointment in a water-washable cream base and as 0.5 per cent prednisolone (free alcohol) combined with 0.5 per cent neomycin in a grease base.

Unlabeled tubes of cream and/or ointment were dispensed depending on whether the lesions were dry, moist, or if primary or secondary bacterial contamination was suspected. Instructions were given that the preparations were to be applied for relief of symptoms only and that special attention was to be paid to promptness and duration of relief from itching. The medication was applied four times a day. Cold cream, U. S. P., was used as a control. Controls were not always feasible; however, whenever possible the paired comparison method of Sulzberger was used, the control

* The trade name of Schering Corp. for topical prednisolone is Meti-Derm.

TABLE I

Summary of Results in Patients Treated with 0.5 per cent Prednisolone Topical Cream

Diagnosis		Total	Satisfactory*	Unsatisfactory
Dermatitis venenata ("contact dermatitis")				
"Housewives' eczema"		25	25	0
All other types		26	26	0
Localized neurodermatitis		6	6	0
Pruritus ani, vulvae		3	2	1†
Disseminated neurodermatitis ("atopic dermatitis")		6	6	0
Seborrheic dermatitis		2	2	0
Benign familial pemphigus‡		1	1	0
Lichen planus‡		5	4	1
Lichen sclerosus et atrophicus‡		1	1	0
Nummular eczema		2	1	1
Bullous dermatophytid		1	1	0
Psoriasis‡		2	2	0
Alopecia areata‡	1			
Insect bite	1			
Pityriasis rosea	1			
Scabies	1	4	0	4
Stasis dermatitis	1			
Drug eruption	1			
Erythema multiforme	1			
Urticaria	1			
Dermographism‡	1			
Purpura‡ (Avitaminosis C)	1	6	6	0
Total		90	83 (92.2%)	7 (7.8%)
Controls		68	16 (23.5%)	

* Satisfactory is defined as prompt and complete relief from pruritus, burning, or pain lasting two hours or more.

† Irritation—1 case.

‡ No effect on underlying disease.

being applied on opposite sides, on other areas, or alternately with the steroid preparations. The ages of the patients varied from 6 months to 75 years, the period of observation from seven days to five months, the average being two to three weeks. Before coming under observation most of the patients had already used other antipruritics, including other topical steroid preparations. No other medication was permitted except that in widespread or acutely inflamed dermatoses, conventional antieczematous, antibacterial, and systemic agents were utilized for a few days. Arbitrarily, a response was considered to be satisfactory if there was prompt and complete relief from pruritus, burning, or pain lasting two hours or more; unsatisfactory, if the response was slow, incomplete, or of short duration. Only those cases are included in which topical prednisolone was used exclusively for a period of one week or more.

RESULTS

The results are summarized in tables I and II. After use of prednisolone cream, 83 (92.2 per cent) of a total of 90 patients obtained complete relief; 7 (7.8 per cent) obtained mild or no benefit. In this group (table I), control cream was utilized by 68 patients, 16 (23.5 per cent) of whom reported equal relief from both preparations. With the prednisolone-neomycin ointment, 30 (81.1 per cent) patients of a total of 37 obtained satisfactory relief, and 7 (18.9 per cent) did not (table II). The control was used by 29, of whom 6 (20.7 per cent) obtained equal relief from both. Eight patients complained of mild burning with the prednisolone cream, which disappeared within a few minutes in most instances; a few patients complained of dryness with the cream—a change to the ointment proved more satisfying. Occasionally, the reverse was true, the cream being more acceptable than the ointment. Among the responsive dermatoses, the effect from prednisolone locally was often dramatic, a single application affording relief all day or all night. Except for the acute, self-limiting dermatoses or in those instances were allergens were identified or removed, recurrences and flares occurred promptly when therapy was discontinued, but these usually responded promptly when topical prednisolone was resumed. Improvement of the dermatosis under treatment paralleled symptomatic improvement except in those cases due to scabies, virus infections, internal disease, or where the cause was unknown. The "eczematized" or secondarily infected, nonspecific disorders re-

TABLE II

Summary of Results in Patients Treated with Topical Prednisolone-Neomycin Ointment

Diagnosis	Total	Satisfactory*	Unsatisfactory
Dermatitis venenata ("contact dermatitis")			
"Housewives' eczema"†	8	7	1
All other types†	3	2	1
Sycosis vulgaris	4	4	0
Psoriasis†	2	1	1
Nummular eczema	2	2	0
Pruritus ani†	1	0	1
Stasis dermatitis†	2	2	0
Disseminated neurodermatitis ("atopic dermatitis)†	3	2	1‡
Impetigo	2	2	0
Seborrheic dermatitis	4	4	0
Dermatophytosis, "id," and moniliasis	4	4	0
Granuloma pyogenicum	1	0	1
Herpes simplex	1	0	1
Total	37	30 (81.1%)	7 (18.9%)
Controls	29	6 (20.7%)	

* Satisfactory is defined as prompt and complete relief from pruritus, burning, or pain lasting two hours or more.

† Secondary infection.

‡ Irritation—1 case.

sponded promptly to topical prednisolone with neomycin without any effect on the underlying disease (psoriasis, lichen planus, etc.).

COMMENT

These results compare favorably with the reports of others who have studied topical use of prednisolone. There were only 2 cases of irritation in this series, 1 each from the cream and the ointment. Kalz and Scott[7] observed that the untoward local effects from water-washable cream bases were less apparent if the cream was used for short periods. It is realized that this report is based on relatively few patients observed under ordinary office practice conditions; possibly, only a few of them used the cream long enough for irritation to appear. Topical use of prednisolone may produce sufficient antiallergic effect to neutralize the undesirable side effects of the cream base. Proof must wait for other and more rigidly controlled studies with prednisolone ointments.

The medical literature on the use, indications, and contraindications of topical and systemic steroid therapy is voluminous and will not be reviewed here. Something should be said of the drawbacks of topical steroid therapy. The medications are expensive and many patients cannot afford them for widespread dermatoses or for long periods. It should be emphasized that we are dealing with powerful drugs and that they are not to be used casually or without medical supervision.[8] In addition, steroids do not "cure" disease, but taking into consideration the indications and potential dangers, they offer safe, maximum, temporary relief when used in conjunction with conventional preventive and therapeutic measures. Few cases of harmful, transepidermal absorption have been reported,[9] but the possibility of adverse systemic reactions from topical steroid is real, and clinicians should be watchful for them.[10, 11]

Hypopyon or corneal ulcer may follow treatment of ocular herpetic infections with topical steroid,[12] and experimental studies suggest that systemic administration of steroids should be avoided the first 7 to 10 days of primary infection because steroids tend to make primary herpes simplex infections worse.[13] Previously, it was thought that hydrocortisone could be applied locally and over wide areas without significant absorption, but Malkinson and Ferguson, using newer methods of measurement, showed absorption to some degree.[14] Schoch reported 3 cases of acute dermatitis repens from hydrocortisone-antibiotic ointment,[15] but no such reaction was seen in this series of patients treated with prednisolone preparations. However, the author has witnessed 2 cases of serous, vesiculobullous dermatitis of the hands that became frankly pustular within 24 hours of systemic steroid therapy.

The previous reports of adverse effects from systemic and topical steroids should not be magnified out of proportion. Tremendous quantities of these agents are being used with relative safety, but it would be hazardous to allow their indiscriminate and uncontrolled use.[16] A recent poll of 100 dermatologists throughout the United States and elsewhere placed topical steroid therapy first on the list of preferred antipruritics[8] and could have inspired the observation of Sutton that "quantities of hydrocortisone have been applied unnecessarily but clinicians as well as patients are

interested in results, strict science, being from the practical standpoint, somewhat tedious."[17]

SUMMARY AND CONCLUSIONS

Prednisolone cream and prednisolone-neomycin ointment are nonirritating and effectively antipruritic, based on the effects observed after topical treatment in a partially controlled group of 127 cases of various itching dermatoses from private practice. Despite the infrequent, although potential, hazards of topical steroids, when used in conjunction with traditional preventive and therapeutic measures, they mark a great advance in the management of skin disorders.

This clinical appraisal may be open to criticism because of inadequate controls, not always feasible in private practice, but the results reported here warrant further and more comprehensive study.

ACKNOWLEDGMENT

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ADVANCED REPORTS FROM CURRENT MEDICAL MEETINGS

This section of the INTERNATIONAL RECORD OF MEDICINE features reports on papers delivered at current medical meetings in the United States and abroad.

International Conference on Poliomyelitis

Geneva, Switzerland.—With official delegates from 30 nations and with physicians, virologists, public health officials, and other scientific representatives from some 50 nations in all, the International Conference on Poliomyelitis met in Geneva, Switzerland, July 8 to 12. Approximately 2000 visitors taxed the capacity of the hotels and meeting places.

The opening session in the famed Victoria Hall, home of the Symphony Orchestra, was conducted by the general chairman, Professor Edmond Grasset, director of the Institute of Hygiene of Geneva's University. Other speakers included Mr. Philip Etter, chief of the Department of the Interior of Switzerland, Mr. Alfred Borel, president of the State Council of Switzerland and of the Canton of Geneva, Mr. Alfred Gigon, president of the Swiss Academy for Medical Sciences, and Mr. Basil O'Connor, president of the International Poliomyelitis Congress. Mr. O'Connor had presided on July 6 at the dedication of the Truman Memorial Library in Independence, Missouri, and arrived by plane just 30 minutes before the opening session of the Conference.

The first scientific session began with reports from the official delegates as to the conditions relating to poliomyelitis in their own countries.

The rest of this session was devoted to vaccination against poliomyelitis, with papers by Jonas Salk, David Bodian, and A. D. Langmuir. Dr. Salk emphasized some of the problems still to be solved including the optimum timing of injections, problems of dosage, and the various vehicles in which the vaccine is administered. "By suitably manipulating dosage and schedule of administration," he said, "an effective degree of immunity can be induced that can be expected to persist for a number of years at least." Dr. David Bodian emphasized that the future of immunization no longer depends on the proof of immunologic theory but rather on the certainty of control of the safety and potency of immunizing products. Dr. Langmuir, of the U.S. Public Health Service, reported that about one hundred million doses of vaccine have been administered since the early phases of the project and the vaccine is safe. Such statistics as are available indicate an effectiveness of more than 75 per cent.

The discussions by such noted virologists as Sven Gard, Sweden, James H. S. Gear, South Africa, Bradford Hill, England, Herdis von Magnus, Denmark, and many others testified to the general acceptance of the killed virus vaccines as a preventive.

The second day's session gave opportunity to the proponents of attenuated poliovirus vaccine to present their points of view, including Hilary Koprowski, Philadelphia, Albert Sabin, Cincinnati, and John P. Fox, New Orleans. Dr. Koprowski described investigations on both monkeys and human beings that established the development of a local resistance in the intestinal tracts of those given attenuated oral vaccines, and showed also that immunity has been developed with durations of one to seven years. After describing his extensive experimentation, Dr. Albert B. Sabin said:

"After mentioning the uncertainties existing about the stability of the lack of neurotropism of these strains, it is concluded that in any country where mass application of the killed virus vaccine is feasible, tests of the above-mentioned viruses

are not justified. If it should be proven that the immunity resulting from formalinized vaccine is of short duration, use of the attenuated live viruses may be considered. In countries where use of killed virus vaccine is not feasible, and when different poliostrains are circulating already these tests may deserve serious consideration."

Dr. Fox reported studies made in Louisiana that indicate that the chance of infection is increased by bad social conditions and the presence of several young children. "Vaccination," he said, "did not influence the number of family infections or the distribution of virus among the population."

The discussions again indicated acceptance of the killed virus vaccine as a preventive, but indicated also many questions still unsolved as to duration of immunity with vaccines of various types and the need for study to improve available preparations.

Speaking for the section of endemoepidemic disease of the World Health Organization, Dr. A. M. Payne found in many countries an increase in susceptibles in adult life. During an epidemic the number of susceptibles changes.

In subsequent sessions special consideration was given to the ECHO viruses and their classification, to the Coxsackie viruses, and particularly to benign aseptic meningitis as a manifestation of infection with ECHO viruses. The number of enteric viruses isolated from human feces is increasing rapidly. Both types of virus in many strains are being found in association with meningitis and in encephalomyocarditis in many countries.

The great broadening of the field of virus study was demonstrated in sessions devoted to tissue culture. Dr. Harry Eagle showed that at least 13 amino acids have proved essential for the survival and growth of all animal and human cells so far examined in cell culture. New techniques for mass propagation of cells were described. From Memorial Hospital, New York, Dr. Alice E. Moore found that cells lines derived from normal sources, when kept in tissue culture, often change and acquire the ability to produce tumors. She said:

"Different nutritional requirements might be a criterion for malignancy, but as yet it is impossible to distinguish cells on this basis. The same is true of a change in virus susceptibility. Another criterion for malignancy was the ability of cultured cells to produce tumors in the homologous strain of animal."

The problems of respiratory distress in bulbar poliomyelitis and in other paralysis affecting breathing are gradually being overcome. "Where once 90 per cent or more of the patients placed in respirators succumbed," according to Dr. Fred Plum of the University of Washington School of Medicine, "it now appears that eight out of ten respirator patients survive their acute illness." Emancipation from the tank respirator to respiratory independence or to lesser respiratory aids is a major goal. New advances in the design of respirators, techniques of management of patients, and improvements in care through the development of respiratory centers have contributed to lower mortality rates. Dr. H. L. Hodes of Mount Sinai Hospital in New York said that with favorable hospital conditions an over-all two year case fatality rate of about 15 per cent among patients with severe respiratory impairment due to poliomyelitis may be expected, while 85 per cent may be expected to survive. Most respiratory patients become independent of the apparatus within six months. In the United States at present, about 1700 patients use such apparatus part of each day.

Profound papers on the natural history of viruses by Dr. Thomas Francis, Jr., of the University of Michigan, Dr. Frank L. Horsfall, Jr., of the Rockefeller Institute, Dr. Max Delbrück of the California Institute of Technology, and Dr. Kenneth M. Smith of the Virus Research Institute in Cambridge, England, indicated the tremendous expansion that is occurring in our knowledge of these tiny particles, which more and more are being indicted as causes of disease.

Several sessions were devoted to the complications of poliomyelitis and to the care of patients severely stricken.

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FOREWORD: A New Policy

The objective of the Quarterly Review of Ophthalmology is to bring together in one publication a concise record of current happenings, both national and international, in this field. Selection and editing of material are designed to prove informative to *the entire medical profession* as well as to ophthalmologists. Manuscripts for the Quarterly Review of Ophthalmology should be submitted to Dr. Arnold S. Breakey, Ophthalmological Foundation, 111 East 59th St., New York, N. Y.

Pseudopapilledema

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Pseudopapilledema is a rare condition, but the importance of knowing that it exists can be shown by the following three cases.

The first was told to me by my late and esteemed colleague, Leslie Paton, and concerned a patient who saw him before she was due to have a cerebral decompression for relief of papilledema, the idea being that if the condition were allowed to persist, consecutive optic atrophy would ensue with resulting blindness. Paton found that the discs were blurred but not swollen, that there was some astigmatism and a defect of muscle balance. He ordered the necessary eyeglasses and sent her to a summer resort for two weeks. As a result, the headaches were cured and the patient was saved from an unnecessary craniotomy.

The second case occurred in a man, R. C., aged 43 years, who two weeks before his visit had had two attacks, beginning with a drawing of the mouth to the right and a curious sensation down the right side of the body. He had also felt unwell for some weeks and had had some dizziness. Visual acuity and fields were normal, but I noted what I took to be physiologic blurring of the nasal side of each disc. An eminent neurologist whom the patient consulted could find no physical signs, but thought the discs were suspicious and that we had to face the possibility of something in the nature of a cerebral tumor. This was in 1924; the discs have remained unchanged ever since and the symptoms disappeared a few years later after the patient had had treatment for pyorrhea.

The third case was a young woman who came to me with a sheaf of notes. I asked her not to show me these until I had examined her eyes because I wished to do so with an open mind. When I looked at her discs I found they had blurred edges and the appearance seemed typical of pseudopapilledema. I then looked at the notes and found that they consisted of letters and even telegrams, some of them several years old, from various ophthalmic surgeons in another country demanding the performance of a cerebral decompression under threat to the patient of ensuing blindness if this were not done.

In addition to these cases, I have recollections, but unfortunately no notes, of many other patients seen at the National Hospital, Queen Square, where a provisional diagnosis had been made of papilledema.

How are these mistakes to be avoided? I would suggest the following points.

This article is part of a series featuring reports from ophthalmologists throughout the world.

1. To have the possibility of pseudopapilledema in mind even if the disc margins are blurred.

2. To measure the amount of swelling. The ability to do this at all accurately is denied by some authorities. Accuracy can however be obtained by practice provided certain precautions are taken. These include having the patient's pupils dilated and accommodation paralyzed, making sure that the vessel one uses for measuring the height of the disc is parallel with that used for the macular region, and securing relaxation of one's own accommodation by using—in the ophthalmoscope—the highest convex lens or the lowest concave one with which the fundus details are just visible. In case of high myopia or astigmatism, it may be advisable to make the measurements while the patient is wearing his correction, tilting the spectacles forward a little to avoid reflections of the source of light. In high myopes there is a possible source of error if a posterior staphyloma should exist, since this may displace the macula backward relatively to the disc.

If practice in taking measurements is required, a good method is to employ the ophthalmoscope to estimate astigmatism, measuring on two vessels at right angles to each other and then checking the result by the usual procedures.

Assuming that the swelling of the disc has been accurately measured, it is usually unwise to be dogmatic about the presence of papilledema unless it amounts to more than 2 or 3 diopters.

3. To realize that the nasal margin of the disc is nearly always less clearly defined than the temporal. This is particularly the case in progressive myopia.

4. To realize the extent of physiologic changes in the disc, especially with regard to its clarity of outline and the size of veins and apparent congestion and tortuosity.

5. The presence of retinal hemorrhages may be of value in the ophthalmoscopic diagnosis between pseudo- and real papilledema, but unfortunately these develop in only about 50 per cent of cases and their presence may be due to other causes. Should they be arranged in lines concentric with the disc margin, however (fig. 1), pseudopapilledema can certainly be excluded. This condition is not often seen and

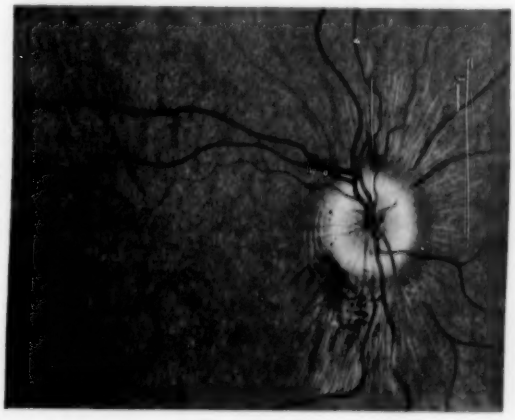

FIG. 1. Papilledema, showing striations of the retina, concentric with the disc margin and outlined in the lower part by hemorrhages.

is due to swelling of the disc laterally as well as anteroposteriorly. The effect of this is to throw the retina into curved folds around the disc margin especially on the temporal side, the hemorrhages settling into the hollows. Even in the absence of hemorrhages, these folds can be seen, as is evident in figure 1, and their presence is valuable evidence of swelling of the disc.

In spite of all these aids, there is a small residuum of cases in which immediate ophthalmoscopic diagnosis is impossible. In the absence of other signs of a space-occupying lesion and if estimation of the cerebrospinal fluid pressure is impracticable, the only course is to wait. Should the fundus appearances remain unchanged over a period of some months, the condition is more likely to be pseudo- than real papilledema.

NOTE: The additional use of visual fields is helpful in differentiating papilledema from pseudopapilledema. In the former condition, the physiologic blind spot is usually enlarged. In the latter, the blind spot is generally normal in size.—EDITOR.

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Unusual Operation Saves Veteran's Sight

An operation in which moisture from the mouth was routed to an eye that was drying up has saved the sight of a veteran, it was reported to the American Medical Association in June. The unusual operation, believed the first ever performed in the United States, involved transplanting the parotid duct to the inside of the lower eyelid, thus changing the flow of a fluid from the mouth to the eye, where the veteran's tear glands had stopped producing the needed eye moisture. Similar operations have been performed in Russia and China, but the American case is thought to be unique because a second operation was necessitated to alleviate excessive moisture in the eye. Both operations were performed by Dr. James E. Bennett, attending ophthalmologist at the Veterans Administration Hospital, Cleveland, Ohio. He was assisted by Dr. Arby L. Bailey, chief resident of ophthalmology at the Hospital.

ABSTRACTS

EYE BANKS AND CORNEAL GRAFTING

24. *Organization and Functions of an Eye Bank.* P. K. BASU AND H. L. ORMSBY. Tr. Canad. Ophth. Soc. *8*:29–33, 1956.

An eye bank was established in Toronto in November 1955. An eye bank should contain an organization for registry of eyes and a laboratory for handling of the eyes. An important part of an eye bank's activities is research, including study of factors related to the obtaining and selecting of donor material, transportation and storage technique, infection, biologic reaction between graft and donor, postoperative care, and the fate of the graft. Information on the scope of corneal grafting should be made available to the profession at large. The lay organization of an eye bank is responsible for directing the patient for treatment.—*Clement McCulloch, M.D.*

NOTE: The importance of eye banks and the growing need for donor material have frequently been stressed by this publication. It is the *responsibility* of the *entire profession* to obtain this material by tactful approach to the next of kin at post-mortem time. Permission for such a donation is printed on the back of all legal post-mortem forms. Technique of removal and methods for preservation may be learned from your local eye bank. If there is none in your area, address the editor for details.—A.S.B.

25. *The Eye Bank and Corneal Grafting Program.* H. L. ORMSBY AND P. K. BASU. Canad. M. A. J. *76*:919–921, June 1, 1957.

The Canadian Ophthalmological Society has authorized the Canadian National Institute for the Blind to undertake the organization of an Eye Bank Service, including publicity to lay groups, registration of donors, and distribution of eyes. In its simplest form an eye bank laboratory consists of a refrigeration system for storage and thermos flasks, which can be packed with ice for shipment of eyes. In 1955 an eye bank was started at the University of Toronto.

Eyes may be removed up to 10 hours after death, stored for up to four days in an ordinary refrigerator at 40 C. The cells of rabbits' corneas remain viable under these conditions up to two weeks. The corneas become cloudy long before the cells become nonviable. At the end of the first week of storage the four globulin fractions of the corneal proteins coalesce into one.

Late clouding of corneal grafts occurs three weeks to two years after grafting in human beings, is unpredictable, and is due to donor-recipient sensitivity. The donor-recipient reaction is a highly specific one and is increased when corneal grafting is done simultaneously with skin grafting.

Thirty-five keratoplasties have been performed by a surgical team working in conjunction with the Toronto eye bank. All have been surgically successful. Ten pa-

tients with severe recurrent metaherpetic keratitis received 10 mm. lamellar grafts with improvement of vision and no recurrences of herpetic infection.

Avian intralamellar skin grafts have been successful. If supplies of human donor eyes become inadequate, clinical trial of avian material would be indicated.—*Clement McCulloch, M.D.*

26. *Corneal Grafts.* M. PLAMONDON. Tr. Canad. Ophth. Soc. *8*:44–54, 1956.

Corneal transplantation was introduced as a regular operative procedure in 1951 at the Hôtel-Dieu de Québec. The number of operations was limited by the number of eyes available. These were obtained from deceased persons after authorization from their nearest relative. Because of Quebec's geographic location, no request was made to the eye bank of the Society for Sight Restoration of the United States. In Canada an eye bank is imperative, but it must have well-directed publicity insisting on the philanthropic aspect and reminding people that the eyes obtained from deceased persons are as good for corneal grafting purposes as those of the living, if the removal is made within the four hour period after death.

Some details of technique described are: a small glass jar to preserve the donor eye from damage, permitting conservation in antibiotic vapors at 4 C., a donor eye support that serves two main purposes, to give back a normal tension to the shrunken hypotensive eye and to provide the necessary fixation. A modification of the bridge cross-stitch is also described: the locking of the two parallel threads prevents their lateral slip and their possible incarceration between the bed and the graft.

Twenty-six corneal grafts were made on 22 eyes, 12 perforating and 14 lamellar. The good results obtained exceed 80 per cent. Four cases were considered unsuccessful even though there was improvement on the former condition. There is still hope for them by retransplant.—*Clement McCulloch, M.D.*

27. *Retinal Breaks in Eye Bank Eyes.* S. T. ADAMS. Tr. Canad. Ophth. Soc. *8*:34–43, 1956.

Eleven eye bank eyes were studied. The fundi were examined by indirect ophthalmoscopy. Pathologic areas were examined under the dissecting microscope and histologic sections were studied. Retinal breaks were found in 3 of these presumably normal eyes. Horseshoe tears and round holes were present and vitreous adhesions were evident. A vitreous membrane ran to the tip of a flap of a horseshoe tear. The retina surrounding both types of breaks showed extensive cystic degeneration.—*Clement McCulloch, M.D.*

PEDIATRICS AND OPHTHALMOLOGY

28. *Orthoptics.* W. P. CALLAHAN. Bull. Hosp. Sick Child. *6*:14–16, Jan., 1957.

This is an introduction to the subject of orthoptics written for physicians interested in pediatrics. There is a discussion of fusion, diplopia, abnormal retinal correspondence, and suppression of 1 eye. The major types of heterophorias and heterotropias are described. The article is extremely readable and is presented in a manner to be

intelligible to pediatricians and physicians outside the field of ophthalmology.—*Clement McCulloch, M.D.*

29. *The Complete Elimination of Retrolental Fibroplasia.* PHILIP BANISTER AND JOHN C. LOCKE. Tr. Canad. Ophth. Soc. *8*:17–28, 1956.

This study of 114 premature infants indicates that it is possible to eliminate retrolental fibroplasia completely. The occurrence of retrolental fibroplasia is due to failures in technique: (a) failure to use an oxygen analyzer regularly, (b) failure to recognize that concentrations of oxygen higher than 35 to 40 per cent are only exceptionally required, (c) failure to realize that concentrations of oxygen below 40 per cent are not always safe, (d) failure to realize that excess oxygen is the only cause of retrolental fibroplasia, (e) failure to realize that prevention of retrolental fibroplasia can be compatible with survival of sick or very small infants requiring oxygen. A list of recommendations for the control of oxygen therapy in premature infants is appended to the article.—*Clement McCulloch, M.D.*

30. *The Results of Organized Ophthalmology in the Americas.* M. E. ALVARO. Tr. Canad. Ophth. Soc. *8*:55–60, 1956.

This article reviews the textbooks, ophthalmologic societies, ophthalmologic journals, established teaching centers, eye hospitals and clinics, organizations for the prevention of eye diseases that have appeared or been active in the Americas.—*Clement McCulloch, M.D.*

31. *Ophthalmological Problems.* J. E. PELLETIER. Tr. Canad. Ophth. Soc. *8*:145–155, 1956.

The field of ophthalmology includes many of the sciences within medicine that apply to the eye. Refraction implies the correction of optical defects of the eye, but also the consideration of pathologic anomalies of the eye. The medical ocular examination and refraction of school children require the services of ophthalmologists. Orthoptic treatments are part of the work of ophthalmologists and should be under their care. The visual aptitude of automobile drivers takes into consideration a number of pathologic defects in the eye, as well as optic abnormalities of the eye. The periodic examination of workmen, and the care of workmen after accidents, should be a responsibility of the ophthalmologist. The needy ought to benefit by ocular care from ophthalmologists, identical to that obtained by other classes in society.—*Clement McCulloch, M.D.*

32. *Traumatic Hyphaema in Children. A Review of 113 Cases.* M. SHEA. Canad. M. A. J. *76*:466–469, 1957.

The incidence of traumatic hyphema (blood in the anterior chamber) is high in children from 6 to 12 years of age. Most secondary hemorrhages occurred on the third or fourth day after the injury. After primary hemorrhage, glaucoma occurred

in 2 per cent of cases, after secondary hemorrhage in 25 per cent of cases. BB gunshot injury was the most common cause of serious ocular damage.

All patients were treated by having complete bedrest, with both eyes bandaged. Neither mydriatic nor miotic agent was instilled. Irrigation of the anterior chamber was considered only as a last resort.—*Clement McCulloch, M.D.*

DIABETIC RETINOPATHY AND THE ADRENALS

33. *The Adrenal Cortex and Diabetic Retinopathy.* S. LERMAN. Tr. Canad. Ophth. Soc. *8*:156–169, 1956.

The 24 hour urinary 17-hydroxycorticosteroid excretion was studied in 39 normal persons, 47 diabetic persons without retinopathy, and 49 diabetic persons with retinopathy. There was no significant difference in the three groups; however, the excretion of 17-hydroxycorticosteroid for the first 24 hours after the administration of compound F was greater in the group of diabetics without retinopathy than in either the normals or the group of diabetics with retinopathy.

By paper electrophoretic technique, the alpha 2 globulin and the alpha 1 globulin in the serum of the three groups of patients were studied. Analysis was made to determine whether there was any correlation between the alpha 2 globulin and the glucosamine levels. The sera of two groups of alloxan diabetic rabbits were studied in the same manner. The mean alpha 2 globulin value was higher in the diabetic with retinopathy than in either of the other two groups. The glucosamine level was higher for the two diabetic groups than for the control group. In the rabbit experiment, the alpha 2 globulin value rose after the administration of cortisone to alloxan diabetic animals. In the control group of animals, none showed the Kimmelstiel-Wilson type of lesion; in the cortisone-treated group, 6 rabbits had definite and advanced renal lesions.

With regard to the hypothesis that an imbalance in mucoid metabolism induced by the diabetic state leads to vascular damage, this study would indicate that further investigation of the complexity of mucoid metabolism is indicated. The study would suggest that alpha 2 globulin levels rise with the severity of the retinopathy and with the development of the Kimmelstiel-Wilson syndrome.—*Clement McCulloch, M.D.*

34. *Hypophysectomy in Unstable Diabetics with Progressive Retinal and Renal Vascular Disease.* LAURANCE W. KINSELL, Oakland, Calif. Bull. New York Acad. Med. 33:171–174, March, 1957.

Hypophysectomy carried out in a small group of diabetic persons with progressive retinal vascular disease has not produced any change in the progress of the disease in patients with advanced pathology, but may possibly be associated with some favorable modification of the vascular degeneration in those with earlier forms of the disease. In view of the variability of progression of the disease in all such patients, critical evaluation of the effects of any therapeutic procedure is most difficult and will require many years of observation. Prophylaxis rather than treatment represents the area of greatest importance.—*Author's abstract.*

35. *Histopathology of the Star-Figure of the Macular Area in Diabetic and Angiospastic Retinopathy.* J. REIMER WOLTER, Ann Arbor, Mich. A.M.A. Arch. Ophth. *57*:376–385, March, 1957.

The histopathology of the "hard" spots of typical macular star-figures of the human retina was studied in 4 eyes with diabetic and angiospastic retinopathy. The spokelike deposits of these star-figures were found to be composed of accumulations of fat-laden phagocytes, remnants of degenerated phagocytes, free lipoids, and hyaline substance. The phagocytes clearly represented retinal microglia that had phagocytized debris of retinal neurons. In many pathologic processes of the retina, the microglia are known to carry phagocytized cellular debris to the blood vessels. In these cases with a star-figure, the microglia were piled up, obviously because of primary changes of the small blood vessels. Many of the fat-laden microglia exhibited advanced degeneration and most of the cellular debris had become hyalinized. This hyaline substance represented large polymorphic patches, most of which were arranged in a spokelike manner in the spaces of the layer of Henle's fibers of the retina. It can be assumed that these hyaline deposits must be largely responsible for the ophthalmoscopic phenomenon of the star-figure.

The "soft" cotton-wool spots in the retina of a fifth human eye were histologically found to be caused by a patchlike degeneration, interruption, and formation of terminal swellings of neurites of the nerve fiber layer of the retina.—*Author's abstract.*

36. *Stress in Ocular Disease.* I. S. TASSMAN, Philadelphia, Pa. Tr. Am. Acad. Ophth. *61*:179–193, March, 1957.

Mental and emotional stress is an important nonspecific factor in the pathoetiology of a number of ocular diseases. Stress is intimately concerned with disturbance of homeostasis in the ocular tissues, particularly in patients with glaucoma. It is also closely associated with dysfunction of the autonomic nervous system and the pituitary-adrenal system in the occurrence of primary glaucoma, hypertensive retinopathy, and diabetic retinopathy, in particular.

The general adaptation syndrome is applicable to certain physiologic functions in the structures of the eye. Some ocular symptoms and diseases fit the pattern of diseases of adaptation. Most of the cases of nongranulomatous iridocyclitis, retrolental fibroplasia, and sympathetic ophthalmia can be regarded as ocular diseases of local stress. They all present evidences of some form of stress involving the ocular structures as an etiologic factor. In cases of central serous retinopathy, collagen diseases involving the eyes, many cases of acute and chronic glaucoma, hypertensive and diabetic retinopathy, stress is important in the etiology and subsequent changes.

The secretion of ACTH and the adrenal hormones in response to chronic stress apparently has a close relationship to the incidence of the retinopathy in patients with vascular hypertension and diabetes mellitus, especially in cases of long duration. These diseases are characterized chiefly by mental and emotional stress, disturbances of the pituitary-adrenal secretions with metabolic and biochemical derangements.

The ever-increasing number of clinical and experimental investigations is evidence of the importance of this subject in ophthalmology and points the way to further

clarification of the complex interaction between the various mechanisms involved.—*Author's abstract.*

37. *Factors in the Pathogenesis of Diabetic Retinopathy.* D. A. ROSEN. Tr. Canad. Ophth. Soc. *8*:122–135, 1956.

The author presents points favoring the thesis that the basic difference between the diabetic with and the diabetic without retinopathy lies in the functional capacity of the adrenal cortex.

Clinical evidence includes: recorded cases of patients treated with cortisone who developed retinal capillary aneurysms, diabetic retinopathy that appeared in nonhypertensive diabetics during pregnancy and cleared after delivery, advanced diabetic retinopathy known to clear after the development of Simmonds' disease, retinopathy described as clearing after hypophysectomy, retinopathy that cleared after adrenalectomy. The use of testosterone has been found beneficial for diabetic retinopathy.

Several types of histopathologic evidence are of interest: Kimmelstiel-Wilson nephropathy is always accompanied by retinopathy, the average weight of the adrenal glands in patients with Kimmelstiel-Wilson's disease is greater than in patients without kidney change, the incidence of vacuolization of the zona fasciculata of the adrenal cortex is higher in patients with Kimmelstiel-Wilson lesions, in cases with nephropathy the incidence of adrenal cortical adenomas is higher than in cases without nephropathy, kidney lesions similar to those in Kimmelstiel-Wilson's disease have been found post mortem in patients who have been given massive doses of cortisone, capillary aneurysms have been found in the retina of nondiabetic patients receiving massive doses of cortisone. Investigative evidence in favor of the thesis is: there is some evidence indicating that the diabetic excretes more 17-hydroxycorticosteroid than does the nondiabetic and that the diabetic with retinopathy excretes more of the steroid than does the diabetic without retinopathy. A higher percentage of diabetics with retinopathy show a substantial drop in eosinophil count after administration of cortisone than do those patients without retinopathy. No evidence could be found that diabetic patients without retinopathy have a primary deficiency in pyridoxine or pantothenic acid. The level of vitamin B_{12} in the serum is higher in the diabetic than in the nondiabetic. The urinary excretion of vitamin B_{12} is higher in the diabetic than in the nondiabetic. This could result from a heightened adrenal cortical activity.

There are several pieces of experimental evidence that support the thesis: glomerular lesions similar to the Kimmelstiel-Wilson lesion may be produced in the rabbit by daily intramuscular injections of cortisone, in alloxan diabetic rabbits the administration of ACTH leads to a substantial instance of the Kimmelstiel-Wilson lesion in the kidney, but it has not been possible to demonstrate capillary aneurysms in the retinas of diabetic animals that received ACTH.—*Clement McCulloch, M.D.*

NOTE: At present there is virtually no treatment for diabetic retinopathy. The recent advent of research into the relationship of the adrenals and retinal changes seems to be a bright ray of hope on a dark horizon. Stress will undoubtedly play a role. —A.S.B.

PSYCHIATRY AND OPHTHALMOLOGY

38. *Human Iris Pigment. I. A Concept of Individual Reactivity with Implications in Health and Disease.* I. KENT. Canad. Psychiat. A. J. *1*:99–104, July, 1956. *Human Iris Pigment. II. Factors in Schizophrenia.* I. KENT, R. G. CHRISTIE, M. M. TUNIS, H. E. LEHMAN, AND R. A. CLEGHORN. Canad. Psychiat. A. J. *1*:105–106, July, 1956.

A series of prostheses have been constructed showing different amounts of color of the iris and forming an iris pigment scale. This scale can be used as a reference when describing the iris pigmentation in any case under consideration. This reference scale provides a guide to determine genetically the color of the iris. An individual's reactivity to his environment may influence the iris pigmentation. The iris pigment scale can be studied in reference to the normal variance that genetically determines mental deficiency and schizophrenia.

The percentage of hospitalized schizophrenic patients in the mixed iris pigment range would be 3 times that of normal subjects.—*Clement McCulloch, M.D.*

NEUROSURGERY AND OPHTHALMOLOGY

39. *Visual Field Defects in Chiasmal Lesions.* H. E. HOBBS. Tr. Canad. Ophth. Soc. *8*:111–121, 1956.

There are a number of lesions about the chiasma that can affect vision. The most common are: pituitary adenoma, craniopharyngioma, meningioma of the sella and of the sphenoidal ridge, and internal carotid aneurysms. Visual symptoms precede other evidence of the responsible lesions, and the visual function should be carefully checked.

Visual damage may for a long time remain predominantly confined to 1 eye. A case presenting uniocular visual defect and having a large saccular aneurysm arising from the right cerebral artery illustrates this point.

Central visual defects may have great localizing value. A case of a meningioma of the cavernous sinus and a case of craniopharyngioma lying behind the chiasma illustrate this point. The method of taking visual fields should be simplified and standardized and suggestions are made on these points.—*Clement McCulloch, M.D.*

40. *Preretinal and Optic Nerve-Sheath Hemorrhage: Pathologic and Experimental Aspects in Subarachnoid Hemorrhage.* DALE C. SMITH, THOMAS P. KEARNS, AND GEORGE P. SAYRE, Rochester, Minn. Tr. Am. Acad. Ophth. *61*:201–211, March, 1957.

Preretinal hemorrhage generally is recognized to be a rather characteristic finding in patients suffering from subarachnoid bleeding. Hemorrhage of the optic nerve sheath probably is as common but is not so well recognized, since it is not visualized ophthalmoscopically. Ballantyne in 1943 first stressed the fact that hemorrhage of the optic nerve sheath, as well as intraocular hemorrhage, is an independent phenomenon that has no direct continuity with the intracranial bleeding that is also present. Walsh and Hedges have recently concurred in this opinion. A study of the

pathologic factors that led also the authors to agree with this opinion is presented. An experimental technique is described in which dogs and monkeys are used. Neither retinal hemorrhage nor hemorrhage of the optic nerve sheath occurred in the dog, but these types of hemorrhage were produced in the monkey. This experimental production of preretinal hemorrhage and hemorrhage of the optic nerve sheath would seem to confirm further the concept that the processes are independent hemorrhagic phenomena.—*Author's abstract.*

41. *Visual Field Defects Following Temporal Lobe Surgery.* S. B. MURPHY. Tr. Canad. Ophth. Soc. *8*:104–110, 1956.

Eight patients on whom temporal lobectomies were performed were studied. Up to 60 mm. of temporal lobe, as measured from the tip, may be removed with either no or minimal resultant field defect. If 55 to 90 mm. is removed, a homonymous superior quadrantanopia will occur. Homonymous hemianopias are likely to be present when more than 80 mm. is resected.

The forward looping of the optic radiations does not reach the tip of the temporal lobe. The fibers originating in the periphery of the inferior homonymous retinal quadrants pass most anteriorly in the temporal lobe. Excision measurements are not absolute, and the position of the optic radiations can be expected to vary from case to case.—*Clement McCulloch, M.D.*

42. *A Case of Organic Tubular Vision.* G. R. MANSFIELD AND J. C. RICHARDSON. Canad. Services M. J. *13*:275–280, May, 1957.

A 36 year old man was shown to have a saccular aneurysm of the anterior cerebral artery. The cerebral aneurysm was clipped. After this his vision was found to be reduced to tubular fields. There were loss of memory, psychosis, diffuse electroencephalographic changes, enlargement of the lateral ventricles.

It is suggested that the field changes are due to occipital infarction resulting from insufficiency of the basilar artery circulation at the time of ligation of the arteries during operation.—*Clement McCulloch, M.D.*

LACHRYMAL SAC SURGERY

43. *Obstruction of the Lachrymal Drainage System: Treatment and Results.* R. L. HALL. Canad. M. A. J. *76*:714–718, May, 1957.

Of 44 adult patients with problems of chronic lachrymal obstruction, 25 were treated by dacryocystectomy and 19 by dacryocystorhinostomy. Patients having dacryocystectomy averaged 17 years older than those in the other group. After operation, the majority of the patients who had dacryocystectomy continued to have symptoms of tearing, while the majority of the patients having dacryocystorhinostomy were symptom-free. Surgical failures after dacryocystorhinostomy became apparent in the immediate postoperative period. It is suggested that consideration be given to the performance of dacryocystorhinostomy in the older patient.—*Clement McCulloch, M.D.*

44. *The Use of Polyethylene Tubing in Dacryostenosis.* W. TURNBULL. Tr. Canad. Ophth. Soc. *8*:136–142, 1956.

Polyethylene tubing is inserted through a cannula into the lachrymal canaliculi. Stitches are placed through the wall of the tubing and through the wall of the canaliculus to be tied on the skin surface. The tubing is left in place indefinitely. Eleven cases are reported—1 case was a failure, in 1 case the patency of the duct was restored but pus continued to be present in the area, and in the remaining cases the procedure was a success.—*Clement McCulloch, M.D.*

MEDICINE AND OPHTHALMOLOGY

45. *Central Retinal Artery Occlusion Associated with Cryoglobulinemia.* RICHARD A. ELLIS, Philadelphia, Pa. A.M.A. Arch. Ophth. *57*:327–334, March, 1957.

Cryoglobulinemia is a condition in which a protein or group of proteins in the blood precipitates on exposure to cold. Cryoglobulinemia is not rare and has been found chiefly in diseases involving the reticuloendothelial system.

The cryoglobulin level may be very variable in the same patient, and no regular relationship has been found between the quantity present and the severity of symptoms. The degree of precipitation varies directly with concentration and inversely with temperature. Increasing the concentration of these proteins leads to an elevation of the temperature at which precipitation begins, and frequently cryoglobulins are noted to start to precipitate at 34 C.

It has been suggested that cryoglobulins, because of their unusual solubility properties, cause stasis and sludging of blood. This may be transient or reversible, as in Raynaud's phenomenon, or may continue causing tissue anoxia, which, in turn, causes more sludging and finally the formation of thrombi. In addition to simple precipitation, which is influenced by concentration of cryoglobulin, the blood viscosity, and temperature, some investigators suggest a sensitivity to precipitated cryoglobulin. This assumes a sensitivity to precipitated protein, which is absent when it is in solution. Others believe that there is a complex mechanism involving infiltration of the vessel wall by cryoglobulins and interference with the formation of thromboplastin and fibrin. These theories may explain how cryoglobulins may possibly act in areas of the body in which there is no change in temperature.

The test for the presence of cryoglobulins is simple. Six to eight cc. of blood is withdrawn from the patient and kept warm. The blood is then centrifuged and the serum specimen removed and put in a refrigerator at 4 C. for 24 to 48 hours. Cryoglobulins are present if the serum becomes cloudy after exposure to the cold. The positive test is confirmed if the cloudy serum then becomes clear when rewarmed to 37 C. The concentration of cryoglobulins is usually estimated from the difference in serum total protein before and after cold precipitation, but many laboratories simply report the test as positive or negative.

A case is reported of a 33 year old Negro man with cryoglobulinemia who developed occlusion of the central retinal artery. He also suffered from cold sensitivity, gangrene of the digits, and scleroderma. It is suggested that a search be made for cold-precipitable proteins in all cases of obscure vascular occlusions.—*Author's abstract.*

46. *A Further Study of Streptococcus Vaccines in Nongranulomatous Uveitis.* ALAN C. WOODS, Baltimore, Md. A. M. A. Arch. Ophth. 56:749–755, 1956.

In this second study of the hypersensitivity to various strains of streptococci shown by patients with various forms of uveitis, the results reported in the first study (*A.M.A. Arch. Ophth.* 50:129, 1953) are confirmed. In these two studies, 198 patients with nongranulomatous uveitis and 188 patients with granulomatous uveitis have been treated intracutaneously with a battery of stock *Streptococcus* antigens (60 strains in all) and with vaccines prepared from any streptococci isolated from their own foci of infection. The incidence of undue bacterial hypersensitivity in the nongranulomatous uveitis patients was 85 per cent, and in the granulomatous uveitis patients it was 27 per cent. In 10 patients with nongranulomatous uveitis, this hypersensitivity was to streptococci isolated from the patient's foci of infection and not to stock strains. Sixteen nongranulomatous uveitis patients reacted both to stock strains and to their autogenous organisms, and 140 patients reacted to the stock strains only. In the majority of instances the patients reacted to multiple strains.

Eighty-six patients with a proved bacterial hypersensitivity were treated intravenously with vaccines composed of the specific strains to which they were sensitive. In 63 per cent of these patients, the treatment was classed as successful, in 15 per cent the patients were improved, while in 22 per cent the treatment was unsuccessful.

The author draws the following conclusions from these two studies: (1) There is a high incidence of hypersensitivity to various strains of streptococci in patients with nongranulomatous uveitis. (2) This hypersensitivity may be either to stock strains of immunologically distinct streptococci or to streptococci isolated from a focus of infection in the patient. (3) Desensitization of the hypersensitive patient with the specific organism to which the hypersensitivity has been demonstrated has given a successful result in a large percentage of patients who were thus treated.—*Author's abstract.*

47. *Uveitis in Association with Rheumatism.* MICHAEL HOGAN, SAUEL J. KIMURDA, AND PHILLIP THYGESON, San Francisco, Calif. A.M.A. Arch. Ophth. 57:400–413, March, 1957.

The occurrence of acute iritis of a recurring type should always lead to investigations for evidence of associated joint disease. The frequent association of the two conditions is more than a chance occurrence. Patients may have unrecognized chronic arthritis of the spine that can be detected only by careful examination and roentgenogram. Fever, elevation of the sedimentation rate, hepatomegaly, splenomegaly, and leukocytosis may help in establishing the final diagnosis.

Rheumatoid iritis occurs in two forms: an acute recurrent one, often affecting one or both eyes, and a chronic one affecting both eyes. The acute variety responds rapidly to topical corticosteroid therapy, whereas the chronic one does not respond to any type of treatment. The chronic form occurs most often in the severer type of joint disease. Ocular involvement may precede onset of joint disease by as much as one to four years.

Juvenile rheumatoid arthritis (Still's disease) frequently has an associated chronic

bilateral iritis that persists in spite of treatment and leads to band keratopathy and cataract.

Reiter's syndrome may have an associated iritis of recurrent type. The joint and eye disease may assume the characteristics of rheumatoid disease with time.

Thirty-eight cases of rheumatoid iritis are described. Thirty-five were of the acute and 3 were of the chronic type. One case of juvenile rheumatoid iritis (Still's disease) is presented. Two cases of Reiter's syndrome and 1 case of gouty iritis are also presented. The patient with gouty iritis had relapses of iritis in association with exacerbation of joint disease.—*Author's abstract.*

48. *Blue Sclerotics with Fragilitas Ossium and Deafness.* B. K. DAS GUPTA, G. C. SEN, AND R. K. BASU, Calcutta, India. A.M.A. Arch. Ophth. 57:435–440, March, 1957.

In this article, the association of blue sclerae with other abnormalities such as multiple fractures, dislocation of joints, laxity of ligaments, and deafness (van der Hoeve's syndrome) is discussed. The cause of the abnormal blue coloration of the sclera—whether it is a qualitative defect due to abnormal translucency of the scleral fibres or a quantitative defect—is not yet settled. The association with fragilitas ossium characterized by unusual brittleness of the bones, which are, therefore, likely to undergo fractures either spontaneously or on trivial injuries, is discussed. Deafness usually affects 60 per cent of subjects with this syndrome and usually occurs after the age of 20. The syndrome shows a definite hereditary and familial tendency. the transmission being of a simple dominant type, and the incidence of this condition in subsequent generations can be predicted by Mendelian Law.

In the article under review 4 cases were examined thoroughly. The family tree was traced through four generations, and the pedigree definitely showed a dominant inheritance. All 4 patients sustained fractures in the upper limbs before puberty, which healed rapidly and uneventfully. Two of the patients developed slowly progressive defects in hearing after the age of 35 (the other 2 are about 20), the cause of which was found to be otosclerosis. All the patients have ½ diopter astigmatism (hypermetropic) in the vertical axis and have some defects in the feet. Biochemical estimation of blood revealed no increase in the serum alkaline phosphatase level. Glucose was found to be below the normal level in all 4 cases. Slight elevation of serum potassium level and ascorbic acid was found in all cases.—*Author's abstract.*

OPHTHALMIC THERAPY

49. *Radioactive Isotopes in Ophthalmology.* EDWIN B. DUNPHY. Bull. New York Acad. Med. 33:310, May, 1957.

In this article is presented some of the background of artificial radioactivity so that a better understanding of its clinical applications might be possible. I have also attempted to review briefly the uses that have been made of the radioisotopes in ophthalmology. The question may now be asked: of how much value have they really been in our field of medicine? In answer, I think we can say that in the realm of ocular physiology they have been invaluable. Because of them, we now know fairly

accurately the rate of aqueous formation, and the old theory of the aqueous being merely a stagnant dialysate has given way to the newer concept of secretion and flow.

In the field of intraocular tumor detection, P^{32} has proved a definite aid to our clinical judgment, provided certain limitations are recognized. It would be premature to say that it is infallible, even in the anterior lesions, until more cases have been studied. It is reasonable to expect that, with the development of better instrumentation, the present difficulties of reaching posterior lesions will be overcome. It is possible that other isotopes may be found to be equally good or even better.

In the field of therapy, with the exception of the beta applicators, the radioisotopes have been disappointing so far, but many unexplored avenues exist and the next few years may bring results undreamed of at the present time—*Author's abstract.*

50. *Antibiotic Therapy for Ocular Infections.* IRVING H. LEOPOLD, Philadelphia, Pa. New York J. Med. *56*:2803–2812, 1956.

There are innumerable antibiotics available for the prevention and active therapy of infections in ophthalmology. There is no doubt that there has been a reduction in visual loss due to infection because of the advent of antibiotics and chemotherapeutic agents, but eyes are still lost today because of the inability to control a variety of ocular infections in spite of vigorous antibiotic therapy.

Failures in therapy may occur because of the improper selection of the route of administration and dosage, because of the improper selection of the antibiotic, or because therapy has been introduced too late.

Prophylactic therapy in potentially infected eyes, such as after a penetrating foreign body or other forms of severe perforating ocular trauma, may be of value. There is some question as to the advisability of prophylactic antibiotic therapy in eyes undergoing intraocular surgery. Antibiotics, when systemically or locally administered, have toxic features. When massive doses have been employed subconjunctivally, toxic features may appear not only locally but also systemically. The ophthalmologist must weigh the advantages to the patient against the risk involved. Prophylactic therapy should be directed against the most likely organisms, which would include the *Staphylococcus*, the coliform bacillus, *Proteus*, *Pseudomonas*, and, occasionally, hemolytic streptococci.

Steroids may be helpful in intraocular infections in cutting down on the inflammatory action and allowing time for the antibiotic to overcome the infecting organism. The smaller the amount of inflammatory action, the less intraocular tissue damage that results and the less subsequent visual loss. Antibiotic therapy alone will sometimes lead to the control of the infectious agent only to have the eye visually lost with the result of marked and severe inflammatory action. Therefore, if some method could be found for reducing the inflammatory action while the specific antibiotic acted, it is conceivable that visual loss might be reduced. For this reason, steroid substances may play a role in intraocular infections—particularly posttraumatic or postsurgical ones.

There are a number of anti-inflammatory agents that are considered to be of value in ophthalmology at the present time. These include phenylbutazone and the various

steroids. The ophthalmologist has for local use cortisone, hydrocortisone, 9 alpha fluorohydrocortisone, prednisone, and prednisolone. In addition, cortisone, hydrocortisone, prednisone, and prednisolone have received widespread use systemically. The newer agents, namely prednisone and prednisolone, are more potent in that smaller doses are required to bring about the same effects as with the earlier forms, such as cortisone and hydrocortisone, but at the same time they do possess toxic features. Although they are not likely to be complicated with edema, this still does occur as do the other steroid side effects, such as psychosis, gastrointestinal symptoms, acne, hypertension, and reduced glucose tolerance. It is well to remember that if there has been failure of response to cortisone, another steroid, such as prednisolone, might be effective and the reverse might also be true.—*Author's abstract.*

51. *Treatment of Chalazia with Systemic Prednisone.* SYLVAN BLOOMFIELD, New York, N. Y. J. Mt. Sinai Hosp. 23:756–760, 1956.

A chalazion basically is a granulomatous tissue response to retained and degenerated meibomian secretions. As such it was thought that corticosteroids might prove effective in its treatment.

Prednisone was therefore administered orally to 11 adults with 17 chalazia. In 16 of these chalazia, significant reduction in size occurred, and in 13, surgery previously indicated became unnecessary. The most satisfactory response occurred in early and inflamed lesions. In a follow-up period of three weeks to three months, evidence of recurrence was observed in only 1 of 11 chalazia successfully treated in this way.—*Author's abstract.*

BOOK REVIEW

Biomicroscopie du corps vitre et du fond de l'oeil (Biomicroscopy of the Vitreous and of the Fundus of the Eye). A. BUSACCA, H. GOLDMANN, AND S. SCHIFF-WERTHEIMER. Paris, Société française d'ophtalmologie, Masson et Cie, Editeurs, 1957.

This 382 page book is a highly technical discussion mainly of the authors' knowledge of the vitreous of the eye obtained with the biomicroscope. It is a beautifully illustrated volume with 40 plates in color depicting the appearance of the vitreous and the fundus of the eye as observed through the biomicroscope, usually with a contact lens.

This book is of particular interest to the ophthalmologist because of the great importance of the vitreous in detachment of the retina and will help him to understand some of the important problems in diagnosis of the detachment of the retina and what he observes after cataract extraction. Those who have special interest in the optic nerve in hypertensive retinopathy, in papilledema, and in optic atrophy will find considerable satisfaction in studying some of the beautiful plates and reading the discussion of these problems.

The French Ophthalmological Society and the authors are to be congratulated for such a scholarly, interesting, and practical presentation of these important problems. —*Conrad Berens, M.D.*

Research in Uveitis

ETIOLOGY--INVASION OR SENSITIVITY? Although approximately 10 per cent of blindness can be attributed to uveitis, the specific etiology of the disease has not been determined with certainty in a majority of cases. Current concepts have been influenced by the investigations of Woods, who has separated uveitis into two distinct groups, the granulomatous and the nongranulomatous. The former is believed to be due to the invasion of the eye by a causative agent in living form, while the latter is often a sterile allergic reaction due to streptococcal hypersensitivity. These concepts are by no means universally accepted. Ashton believes that this classification is unsatisfactory because the histologic reactions are simply those of acute and chronic inflammation and no sharp distinction can be made between them.

THREE APPROACHES TO RESEARCH. Three major facets of uveitis research are: (1) an attempt to isolate an infectious agent, (2) the use of diagnostic immunologic procedures on aqueous and serum, and (3) the experimental production of uveitis in animals. Although many causative agents have been readily identified in the uveal tract, the demonstration of a filterable virus in an eye with uveitis has been generally unsuccessful. However, the recent isolation of a virus in Behcet's syndrome and the reproduction of the disease by animal inoculation have stimulated investigation along this line. While the experimental production of uveitis in animals is not new, the recent application of improved procedures promises to increase our understanding of the basic underlying processes. The use of Coons' fluorescein labeled antibody technique for the eye has demonstrated plasma cell production of antibodies. Tagging of antigen with radioisotopes facilitates a correlation of the transfer and localization of antigen to the clinical and pathologic course of the disease. However, in experimental investigations of this type, it is important to consider the possibility that fundamental differences exist between the clinical disease and the experimentally induced condition.

MANY QUESTIONS REMAIN UNANSWERED. Many basic questions remain unanswered. In cases of hypersensitivity, what is the nature of the allergens and how are they produced? What

factors determine the presence of inflammation in the eye and the absence of inflammation in other organs? How important is autoimmunization? To what extent are the antibodies locally or systemically produced and are these antibodies from both sources similar? When one considers that allergic or immunologic reactions are determined by cell responses to foreign substances and that these responses probably represent a basic property of living cells, the complexities of the problem are readily apparent.

Ralph Z. Levene, M.D.
New York, N. Y.

Report on Phospholine Iodide

Phospholine iodide was tested in 101 glaucomatous eyes and successfully controlled the condition in 73 of them, reported Drs. Irving H. Leopold, David Gold, and Paul Gold, Wills Eye Hospital, Philadelphia. Although 25 cases were recorded as failures, in 12 of them the pressure was controlled but the drug was discontinued because of bad side effects, including brow aches, dimness of vision, an unusual rise in pressure in 2 cases, nausea in 1. The drug controlled 42 cases that had not been helped with currently used solutions.

Questions and Answers

Q. *Is vascular hypertension a contraindication for cataract surgery?*

A. Increased blood pressure during and after surgery for cataract may result in several complications, e.g., capillary hemorrhages in the operative area or subchoroidal hemorrhages leading to prolapse of the iris, lens, vitreous, and in rare cases to expulsive hemorrhage. Elevation of diastolic blood pressure above 100 mm. Hg. is considered frought with danger. Systolic hypertension in the presence of normal diastolic pressure is less dangerous, particularly if it can be improved by sedation and bedrest. The possibility of coexisting organic vascular changes should be kept in mind and capillary fragility tested.

Q. *Claims have been voiced that eye exercises improve vision in myopia. Is this true?*

A. The effects of eye exercises and visual training on myopia have been investigated for many years. They have been praised by some and condemned by others. No unanimity of opinion prevails. However, recent studies, including adequate controls, would seem to indicate that in the presence of sufficient motivation on the side of the patient, a specific course of visual training may improve visual acuity, size of the visual field for form, refractive error, and reading speed in selected individuals.

Q. *Which alkali should be used when first aid is administered to a person whose eye was burned with sulfuric acid?*

A. In chemical eye injuries, neutralization of acid by alkali and vice versa is today considered obsolete because it is time-consuming and therefore dangerous. Speed in the removal of the offending substance is most important. Instant copious irrigation with water, which is almost always available, is the rule in first aid regardless of the chemical. Topical anesthetic solution may be instilled, if available. In its absence the eyes must be forced open because pain causes spasm of the lids. Irrigation should be continued for at least 10 minutes, after which time dry sterile dressing is applied (no ointments!), and the patient should then be referred to an ophthalmologist.

Q. *What is the percentage of good results in corneal transplants?*

A. It depends on the selection of cases for this operation. If only cases with reasonably good prognosis are considered, the surgeon may obtain about 75 per cent of good results. If the surgeon operates even when chances of success are remote, the percentage of good results may drop to 15 or less. Generally, with repeated keratoplasty, chances of success are greater.

Q. *Should an eye with conjunctivitis be covered with a dressing?*

A. In conjunctivitis without corneal involvement dressing is contraindicated. It causes accumulation of the secretion in the conjunctival sac, which may result in secondary corneal involvement. Frequent irrigations with mild antiseptic solutions are beneficial. In addition, heat created by the dressing frequently increases the amount of secretion in conjunctivitis (especially in purulent forms). Cool com-

presses are, therefore, advantageous. The opposite is true in cases with associated corneal involvement. Dressing and heat are often indicated.

Q. *Is there any new satisfactory treatment for retinitis pigmentosa?*

A. The evaluation of treatment in this disease is rather difficult because of the natural fluctuation in the progress of this disease. Several remedies have been advocated during the past few decades, but most, if not all, of them have been subsequently discredited. At present, the use of bishydroxycoumarin has shown some promising results. According to the investigators, no patient has been made worse by the treatment, and improvement was noted in 80 to 90 per cent of patients, ranging from that noticeable only by the patient to marked improvements in visual acuity and visual fields. Those who have been helped reportedly maintained their gains. The investigations with bishydroxycoumarin and other anticoagulants continue. Whether the improvements will be lasting and consistent remains to be seen.

Q. *Is staining the cornea with fluorescein a safe procedure?*

A. Solutions of fluorescein easily become contaminated with *Pseudomonas aeruginosa* (*Bacillus pyocyaneus*). If such a contaminated solution is instilled into an eye with epithelial defect of the cornea, it may result in rapidly destructive corneal ulcer, followed by endophthalmitis. Until several years ago these eyes were almost invariably lost. Today many of them are saved with antibiotic treatment.

This complication of an otherwise innocuous staining procedure can be obviated by the use of individually packed sterile fluorescein strips, which have recently appeared on the market.

Q. *A middle-aged woman continually complains that her eyes water. At no time have excessive amounts of tears been observed. There is no discharge or excessive redness of the eyes. Various eye drops were prescribed (zinc, sulfa, antibiotics, steroids) without lasting success. What would you suggest?*

A. Methylcellulose, ½ to 1 per cent solution, might be the answer. Many patients complain of excessive tearing when actually deficient secretion of tears causes their symptoms. Dryness of the conjunctiva and cornea seems to be becoming more prevalent in recent years. Etiology is not always known. It may be an idiopathic condition or represent part of the Sjögren's syndrome (keratoconjunctivitis sicca) found in middle-aged patients in association with arthritis. It may be a sign of pathologic conditions of the lachrymal gland and many other more serious diseases.

Amount of tears secreted can be estimated fairly accurately by measuring the length of the moistened part of a filter paper strip hooked onto the lower lid for five minutes (Schirmer's test).

Q. *Enucleation was suggested to one of my female patients. She refuses to have it done for fear of cosmetic handicap in her work. Her sister had 1 eye enucleated many years ago and the prosthesis doesn't move at all, the upper lid sinks, etc. Is there any other way in which this woman could be helped?*

A. No definite advice can be given without knowing more about your patient's

condition. However, when no contraindications exist (and there are few), the evisceration of the eyeball can be performed rather than enucleation. It consists in removing the cornea and all contents of the eyeball, followed by insertion of a special plastic implant over which the sclera is tightly closed. Results seem to be superior to those of enucleation. The operation is less traumatic; the extraocular muscles are left undisturbed, thereby ensuring more normal mobility of the stump with the properly fitted prosthesis. There is also less likelihood of atrophy of the orbital tissues with subsequent sinking of the upper lid.

Q. *Is it advisable to use vasoconstrictors in conjunctivitis?*

A. That depends on the type of conjunctivitis. Theoretically, vasoconstrictors should not be used in infectious types because reduction of blood circulation limits the supply of the patient's own antibodies, thus impairing the protective mechanism of the body, particularly important in viral disease. In practice, weak vasoconstricting solutions may be helpful by relieving subjective complaints. In addition, constriction of the conjunctival vascular bed slows down the absorption into the blood stream of the active bacteriostatic or bactericidal substances introduced into the conjunctival sac, prolonging the time of their activity. Since the application of modern ophthalmic vasoconstrictors is not followed by reactive vasodilatation, they bring comfort to the patients, particularly in allergic conjunctivitis (although the modern ophthalmic armamentarium includes more efficient drugs for that purpose) and in cases of stenosis of the nasolachrymal duct; in the latter condition, tear drainage is promoted by the reduction of the hyperemia of the blood vessels of the mucous membranes with subsequent enlargement of the duct lumen.

George Z. Carter, M.D.
New York, N. Y.

NOTE: Questions from our readers are invited. Address George Z. Carter, M.D., Ophthalmological Foundation, 111 East 59th St., New York, N. Y.

Tonometry Aids in Detecting Glaucoma

Routine tonometry during the course of physical examination can uncover many cases of previously undetected early glaucoma and help stop the increase in blindness in older persons. In a study made at the University of Tennessee College of Medicine, tonometry performed on 1210 persons over 40 turned up 44 cases of glaucoma. In 11 southern California towns, 5023 persons over 40 received preliminary tests and 505 were tested a second time. Glaucoma was found in 124 of these 505.

CASE REPORT

Herpes Zoster Ophthalmicus

A 42 year old man was seen in the office with complaints of pain and photophobia in the left eye of four days' duration.

Examination of the patient revealed some lid edema and minimal ciliary and conjunctival injection. Visual acuity uncorrected was 10/400 in the right eye (due to an old gunshot injury) and 20/20 in the left eye. The cornea was clear and the ocular tension was normal. A slit-lamp examination revealed a faint flare with a few cells in the anterior chamber. The remainder of the eye examination and the past medical history were not remarkable. The treatment instituted was 1 per cent aqueous atropine solution topically twice daily for the mild iridocyclitis.

Two days later the patient had developed a well-demarcated eruption of vesicles on the scalp, forehead, lids, and nose along the distribution of the ophthalmic branch of the left trigeminal nerve. Many of the vesicles had become secondarily infected as they were purulent. The regional lymph nodes were enlarged and tender.

Examination of the left eye revealed a few vesicles of the cornea peripherally and a generalized increased relucency of the entire cornea. There was also a 3+ aqueous flare. A diagnosis of herpes zoster ophthalmicus with secondary infection complicated by keratitis and iridocyclitis was made, and the patient was hospitalized. Therapy consisted of tetracycline-nystatin combination,* 250 mg. every six hours, and atropine, 1 per cent topically to the left eye three times daily. The secondary infection was controlled by the fourth hospital day and the eye complications had subsided; the patient was discharged on the fifth hospital day.

One week after discharge from the hospital the patient developed a severe episcleritis temporally adjacent to the limbus of the cornea. The contiguous cornea was thickened and clouded, and subsequently a deep undermined ulcer developed at this site. The latter was thought to be a trophic disturbance. The topical atropine solution had been continued. In addition, 0.5 per cent prednisolone-neomycin† ophthalmic solution topically every two hours was prescribed. Within six days the episcleritis and cornea had healed.

Seven weeks after the onset of the infection, the visual acuity had returned to normal and the only sequela was some residual scarring of the involved cornea and skin.

Herpes zoster ophthalmicus is an acute viral infection of the gasserian ganglion. One episode gives permanent immunity. The virus of herpes zoster is closely re-

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EDITOR'S NOTE: This section will be devoted to case histories of typical daily problems in the eye field. It is designed to help the reader toward a better understanding of diagnoses and treatment in ophthalmology.

* The trade name of E. R. Squibb & Sons Division, Olin Mathieson Chemical Corp., for tetracycline combined with nystatin is Mysteclin.

† The trade name of Merck Sharp & Dohme for prednisolone-neomycin solution is Neohydeltrasol.

lated to the varicella virus. The infection is always associated with a neuralgia, which is often excruciating, and the postherpetic neuralgia may be bothersome.

The ocular complications include keratitis, iridocyclitis, uveitis, muscular palsies, and optic neuritis. Systemic corticosteroids and corticotropins should be reserved for severe cases as they may increase the severity of the usually coexisting herpes zoster encephalitis.

Dahar Cury, M.D.
Huntington Park, Calif.

News and Notes in Ophthalmology

Retrolental fibroplasia can now definitely be wiped out among premature infants, declared Dr. Franklin M. Foote, executive director of the National Society for the Prevention of Blindness, at the joint session of the Pan-American Association of Ophthalmology and the N.S.P.B. Use of high oxygen concentrations in incubators immediately after World War II led to growth of the disease, Dr. Foote said, but in the past four years a limit of 40 per cent oxygen concentration has been increasingly enforced, with resultant disappearance of the disease where this has been done.

Successful use of eye tissue in corneal transplants after preservation for as long as two years was reported by Dr. John Harry King, Jr., consulting ophthalmologist to the U. S. Surgeon-General. The eye tissue is dehydrated in glycerine and stored at room temperature, remaining viable for an indefinite period of time, while corneas treated conventionally become useless within a few days after removal from the eye of the donor, he said.

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